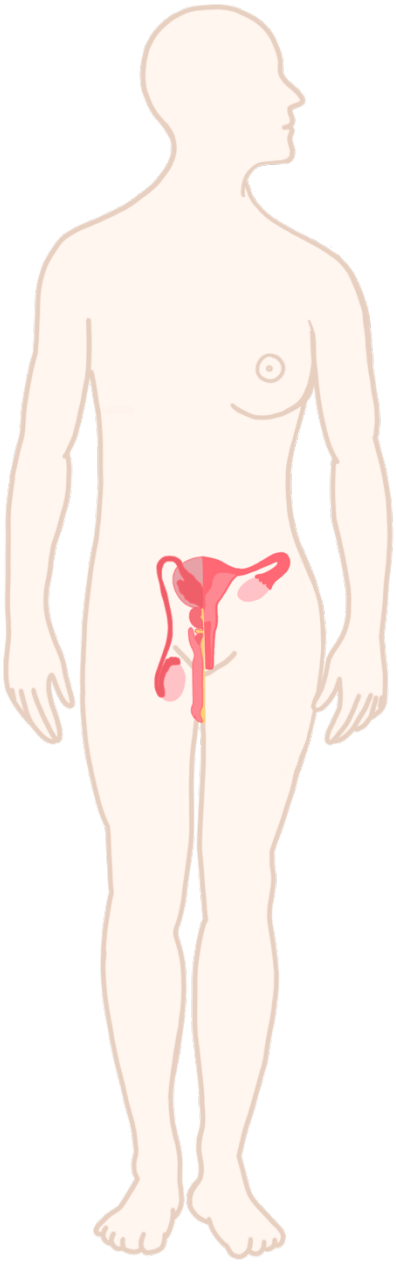


Reproductive Pathology

Marthe Abrahamsen • Zosia Frączek

First Edition
May 2021
Copyright StudyAid 2021

Authors
Zosia Frączek
Marthe Abrahamsen

Editors
Alexandra Vedeler
Ida Marie Lisle

Illustrators
Alexandra Vedeler
Nora Charlotte Sønstebø
Ida Marie Lisle

Booklet Disclaimer

All rights reserved. No part of this book may be reproduced in any form on by an electronic or mechanical means, without permission from StudyAid.
Although the authors have made every effort to ensure the information in the booklet was correct at date of publishing, the authors do not assume and hereby disclaim any liability to any part for any information that is omitted or possible errors. The material is taken from a variety of academic sources as well as pathology lecturers, but are further incorporated and summarized in an original manner. It is important to note, the material has not been approved by professors of pathology.

All illustrations in the booklet are original. This booklet is made especially for students at the Jagiellonian University in Krakow by tutors in the StudyAid group (students at JUMC).
It is available as a PDF and is available for printing.
If you have any questions concerning copyrights of the booklet please contact studyaidkrk@gmail.com.

Studyaid is a transgender friendly organization. In this booklet, the usage of female/woman/girl and male/man/boy refers to internal and external genitalia, as this is booklet is based on anatomical and physiological sex. Naturally, people may either identify or fully transition into a different gender. However, this is beyond the scope of this booklet and JUMC exams, so we will not be covering that information here.

About StudyAid

StudyAid is a student organization at the Jagiellonian University in Krakow. Throughout the academic year we host seminars in the major theoretical subjects: anatomy, physiology, biochemistry, immunology, pathophysiology, supplementing the lectures provided by the university. We are a group of 40 tutors, who are students at JU, each with their own field of specialty. To make our seminars as useful and relevant as possible, we teach in an interactive manner often using drawings and diagrams to help students remember the concepts. In addition to most seminars we create booklets, on which the seminars are based to aid the students in following the presentations. If you have any questions, do not hesitate to contact StudyAid at www.studyaid.no, we are always happy to answer any questions you may have academically related or not.

Table of Contents

PART 1 – FEMALE REPRODUCTIVE SYSTEM 4

Section 1 – The Vulva 6

Section 2 – The Vagina 11

Section 3 – The Cervix 15

Section 4 – The Uterus 20

Section 5 – The Ovaries 28

Section 6 – The Breast 36

Section 7 – Female Infertility 41

Section 8 – Gestational Pathologies 45

PART 2 – MALE REPRODUCTIVE SYSTEM 48

Section 1 – The Penis 50

Section 2 – The Testis and Epididymis 57

Section 3 – The Prostate 71

Section 4 – Male Infertility 84

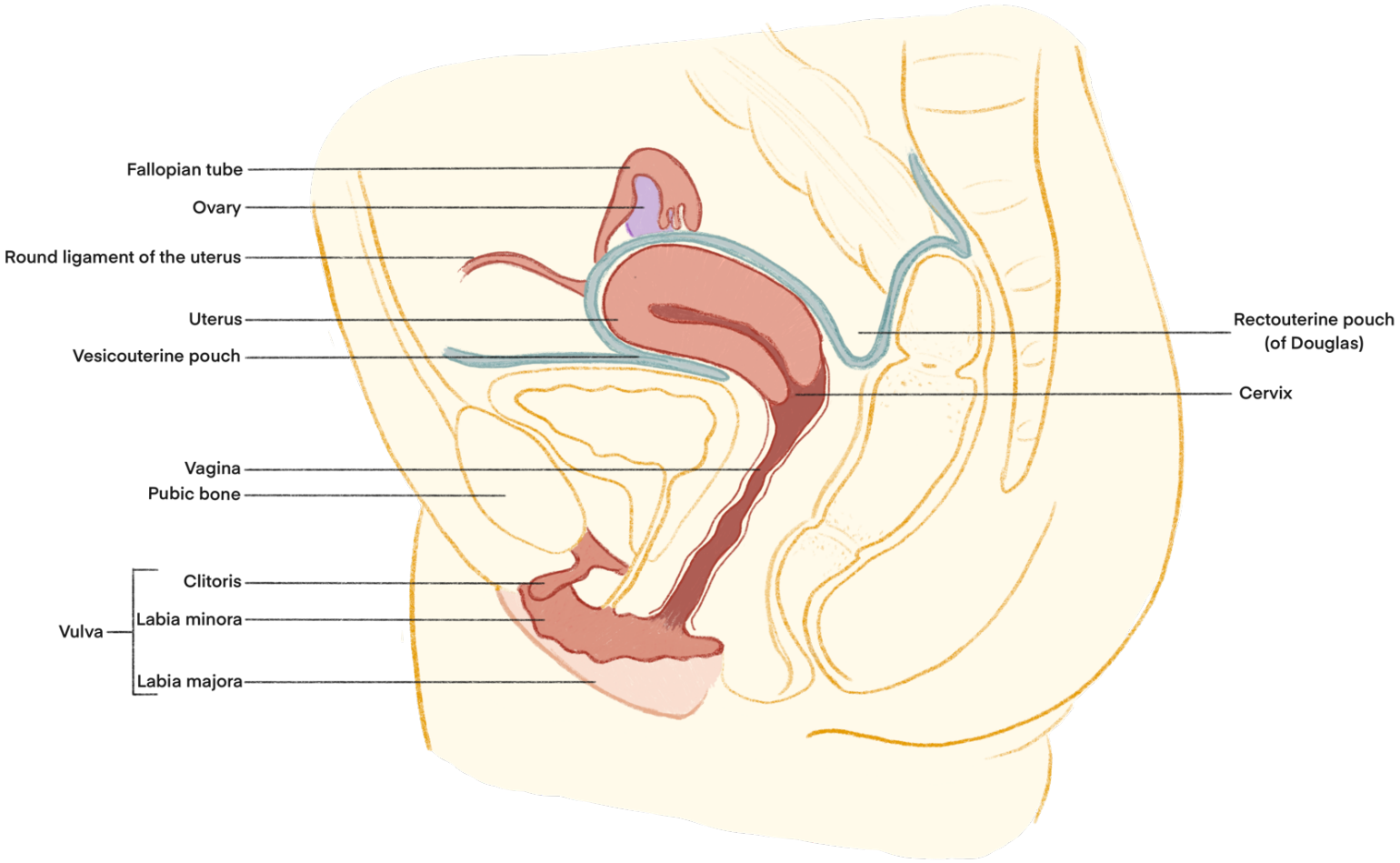
PART 3 – SEXUALLY TRANSMITTED INFECTIONS 91

Section 1 - Bacteria 92

Section 2 – Viruses 99

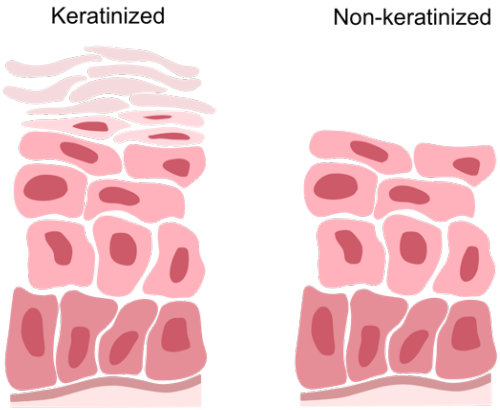
PART 1 – FEMALE REPRODUCTIVE SYSTEM

Review of female reproductive anatomy



Section 1 – The Vulva

1.1 – Overview
1.2 – Bartholin Cyst
1.3 – Condylomas of the Vulva
1.4 – Lichen Sclerosus
1.5 – Lichen Simplex Chronicus
1.6 – Carcinomas of the Vulva
1.7 – Test Yourself



1.1 – Overview

- The vulva is the external part of the female genitalia.
- It includes the labia major and minora, clitoris, vestibule (opening to the vagina) and urethral orifice.
- The structures of the vulva are lined by keratinized or nonkeratinized stratified squamous epithelium, except the vestibule, which is lined by nonkeratinized simple squamous epithelium.

1.2 – Bartholin Cyst

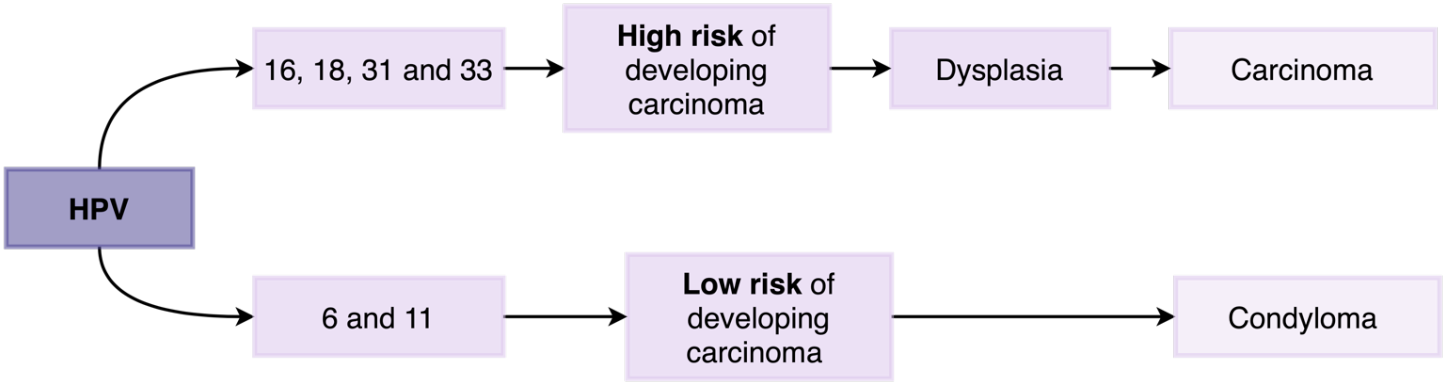
- Two glands called Bartholin's glands, are found at the entrance to the vagina.
- These glands are responsible for secreting mucous during sexual arousal.
- As mentioned earlier, inflammation of the vulva can lead to a blockage of the glands.
- When a duct becomes blocked, the fluid produced within the glands cannot escape, and the gland and duct will dilate.
- The result is the formation of a cyst, which may become infected and develop into an abscess.
- A Bartholin cyst is usually seen unilaterally and affect women of reproductive age.

1.3 – Condylomas of the Vulva

- *Condyloma acuminatum*, also called genital wart, can develop on the lower parts of the female reproductive tract, including the vulva, vagina and cervix.
- These warts are caused by the *Human Papillomavirus (HPV).*
- More than 40 types of HPV that can infect the genital tract, have been identified.
- We can distinguish between those that cause benign condylomas and those that can cause squamous intraepithelial lesions and/or carcinomas.

I. HPV related lesions

- Genital warts: Benign lesions caused by HPV types 6 and 11
- Cervical carcinoma and squamous intraepithelial lesions are associated with HPV strains 16, 18, 31 and 33, which are known as high-risk.



CLINICAL CORRELATION

HPV vaccines

- There are vaccines available that protect against the HPV virus.
- Gardasil® protects against type 6, 11 16 and 18.
- Cervarix® protects against type 16 and 18

1.4 – Lichen Sclerosus

- Lichen sclerosus is a chronic inflammatory disease.
- Previously known as *lichen sclerosus et atrophicus*
- The incidence peaks in post-menopausal women and prepubertal girls.
- The lesion itself is benign but it carries a slight increased risk of developing into squamous cell carcinoma.

I. Characteristics

- Thinning of the epidermis.
- Skin changes with accompanying pruritus.
- White and atrophic patches known as leukoplakia can appear on the labia major and minora.

II. Etiology

- The exact cause is unknown, but it is assumed that genetic, hormonal and immunologic mechanisms play a role in the development of lichen sclerosus.
- Autoimmune mechanisms are also likely, as many of the affected patients also suffer from autoimmune thyroid disorders, diabetes mellitus type 1 and alopecia areata.

III. Pathomechanism

- A T-cell activation in the deeper levels of the dermis leads to a chronic, progressive inflammation.

1.5 – Lichen Simplex Chronicus

- Lichen simplex chronicus is a secondary skin lesion associated with prolonged scratching of the skin and atopic dermatitis.
- Well-demarcated, erythematous or hyperpigmented plaques can be seen on the vulva.
- The lesion is benign but can be found on the margins of vulvar cancers.

I. Characteristics

- Thickening of the epithelium
- Hyperkeratosis

CLINICAL CORRELATION

Atopic dermatitis

- Atopic dermatitis is a chronic, pruritic inflammatory skin disease that often affects children.
- The pathomechanism involves a hypersensitivity reaction where the immune system attacks the skin.
- Typical findings are dry skin and severe pruritus.
- It is often associated with allergic rhinitis and asthma.

1.6 – Carcinomas of the Vulva

- Carcinoma is a cancer that develops from epithelial cells.
- Vulvar carcinoma is rare, and account for about 3% of all cancers that involve the female reproductive tract.

I. Types

- Squamous cell carcinoma is the most common type of vulvar carcinoma.
- Other tumors include melanoma, basal cell carcinoma and Bartholin gland adenocarcinoma.
- Human papillomavirus infections are associated with the majority of vulvar squamous cell carcinomas.
- We often distinguish between vulvar carcinoma that is caused by HPV and vulvar carcinoma that is associated with long standing lichen sclerosus.

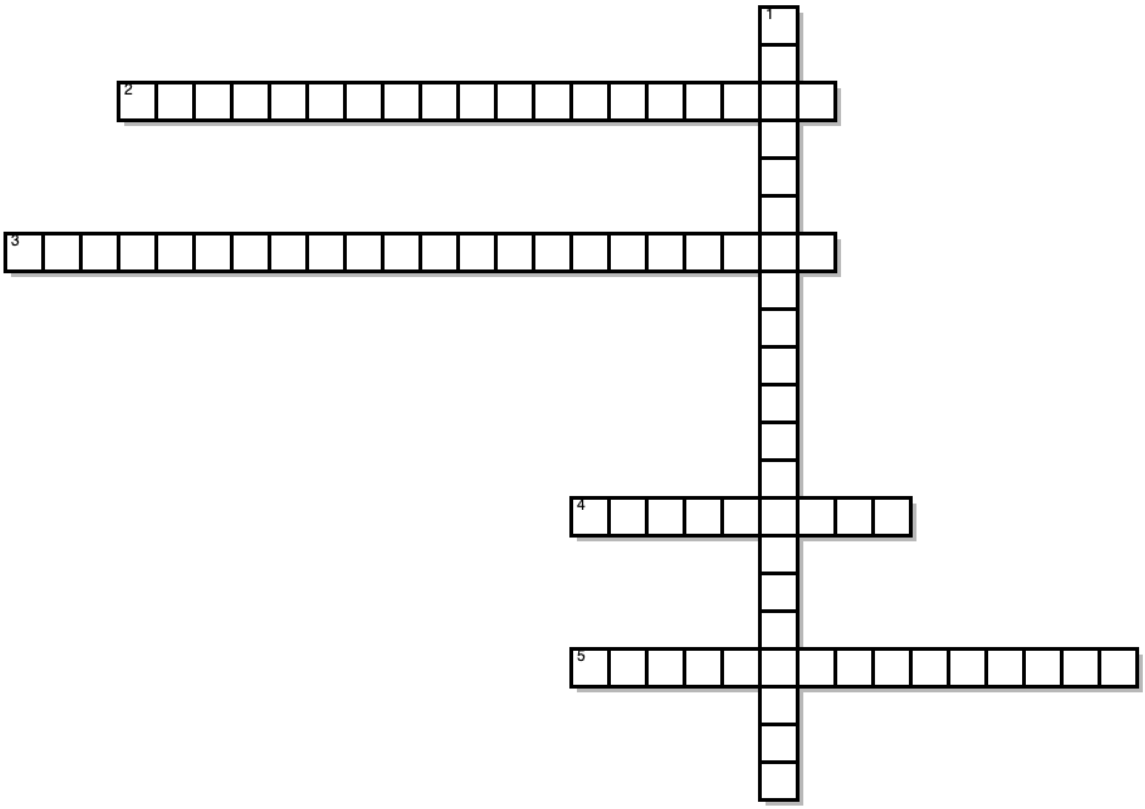
Etiology	Morphology	Presentation	Risk factors	Epidemiology
HPV-related	Poorly differentiated Multifocal	Leukoplakia[1]	Cigarette smoking Immunodeficiency	Middle-aged women
Non-HPV related	Well differentiated Unifocal	Differentiated vulvar intraepithelial neoplasia (dVIN)	Genetic factors Autoimmune disease	Most commonly occurs in older women

[1]White and defined patched on the mucous membrane.

III. Extramammary Paget disease

- Paget disease of the breast is a rare condition associated with breast cancer. *Extramammary Paget disease (EMPD)*, is an interepithelial adenocarcinoma of the vulva with a similar clinical picture as Paget disease of the breast.
- It most commonly affects women >60 years of age.
- Clinical presentation: Pruritus and has an eczematous appearance with well-demarcated and raised borders.
- The risk for underlying invasive EMPD is low, unlike Paget disease of the breast, which is always associated with carcinoma.

1.7 – Test Yourself



ACROSS

2 Lesion caused by HPV
3 Associated with atopic dermatitis
4 Increased risk of developing vulvitis
5 Thinning of the vulvar epidermis

associated with autoimmune mechanisms

DOWN

1 Most common type of vulvar carcinoma

Section 2 – The Vagina

2.1 – Vaginitis
2.2 – Vaginal Cancer
2.3 – Test Yourself

- The vagina is a muscular canal that extends from the vulva to the cervix.
- It is covered by non-keratinizing stratified squamous epithelium.

2.1 – Vaginitis

- The terms vulvitis, vaginitis and vulvovaginitis all refer to the same disease in the clinical setting. We will use vaginitis here.
- Most commonly caused by infectious agents
- Characteristic symptoms include:
    1. Itching and a burning sensation
    2. Changes in odor
    3. Vaginal discharge

CLINICAL CORRELATION

Vaginal flora
The normal vaginal flora has a pH from 4.0 to 4.5. An increase in the pH can lead to overgrowth of pathogenic bacteria.

I. Pathogenesis and etiology

- Disturbances in the vaginal flora can lead to vaginitis.
- *Lactobacillus* is a part of the normal vaginal flora, where it converts glycogen into lactic acid, which decreases the pH of the vagina. The acidic vaginal flora prevents an overgrowth of pathogenic bacteria.

Etiology	Agent	Comment
Infectious causes[1]	Protozoan parasite	*Trichomonas vaginalis*, may be called trichomoniasis
	Fungus	*Candida albicans*
	Bacteria	Bacterial vaginosis is caused by shift in the vaginal microbiota towards bacteria in such as *Gardnerella vaginalis*, *Prevotella* species and *Mycoplasma hominis*
Combination	Foreign body	Retained tampons or condoms
Non-infectious causes	Allergens/irritants	Soap, latex allergy, vaginal douching
	Menopause	Atrophic vaginitis

[1]Bacterial vaginosis, infection with *candida albicans* and *trichomonas vaginalis* account for over 90% of the infectious causes of vaginitis

2.3 – Vaginal Squamous Cell Carcinoma

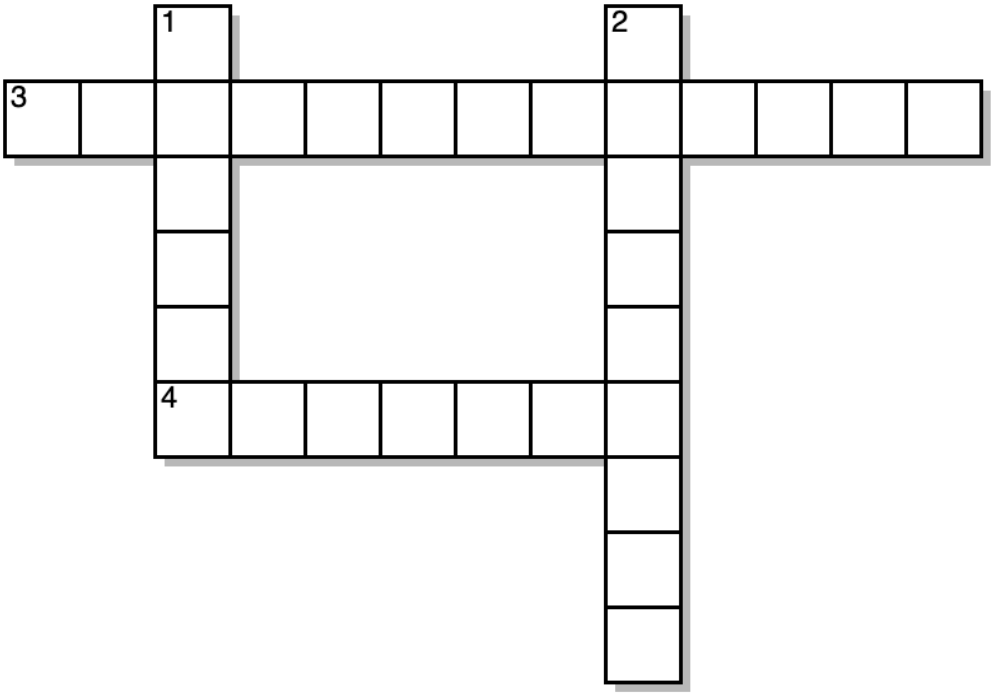
- Most common type of vaginal neoplasm, 90% of all vaginal carcinomas are squamous cell carcinoma.
- Age: > 60 years
- VAIN: vaginal intraepithelial neoplasia is a precursor lesion for squamous cell carcinoma. It is nearly always associated with infection of a high-risk type HPV.
    1. Arises from native squamous epithelium in the vagina, not from metaplastic changes which is the case in cervical intraepithelial neoplasia (CIN)
- Only considered primary vaginal cancer if the cervix is uninvolved
- May appear 5-6 years after radiation treatment for cervical carcinoma
- Associations: neoplasms of lower genital tract
- Metastases:
    1. Regional iliac nodes
    2. Inguinal nodes
    3. Lung
    4. Bone
- Survival: 40% survive longer than 5 years

Other tumors of the vulva and vagina

Angiomyofibroblastoma	- Benign, well circumscribed vulvar tumor - Alternating hypercellular and hypocellular areas - Spindle cells - Plump stoma cells with eosinophilic cytoplasm that aggregate around small blood vessels - Treatment is removal of tumor
Fibroepithelial polyp	- Benign hormone induced hyperplasia of loose subepithelial connective tissue - Central fibrovascular core covered by squamous epithelium
Mullerian papilloma[1]	- Rare, benign polypoid lesion of the cervix or vagina
Aggressive angiomyxoma	- A rare mesenchymal tumor - Slow growing, gelatinous, ill-defined perineal lesions - May provoke the formation of a *Bartholin cyst*
Vaginal cysts	Epithelial inclusion cysts - Lined with squamous epithelium - Risk factors: trauma and surgery Gartner duct cyst - Location: Lateral vaginal wall - Non-mucin secretion - May give rise to *malignant mixed tumor of vagina* Mullerian cyst - Columnar cells that secrete mucin - Focal squamous metaplasia Urothelial cysts - Location: Periurethral and Skene glands
Vaginal intraepithelial neoplasia (VAIN)	- Derived from squamous epithelium - Affects upper 1/3 of the vagina - Multifocal lesions (50%) - Associated with other reproductive neoplasms
Leiomyosarcoma	- Malignant tumor - Recur locally - Poor differentiation results in poor prognosis
Rhabdomyosarcoma	- Embyonal or botyroid subtype malignant tumor - Most common malignant soft tissue tumor in *children and adolecents*

[1]Mullarian papilloma = mesonephric papilloma = intramural papilloma

2.4 – Test Yourself



ACROSS

3 Part of the normal vaginal flora
4 A fungus that can cause vaginitis

DOWN

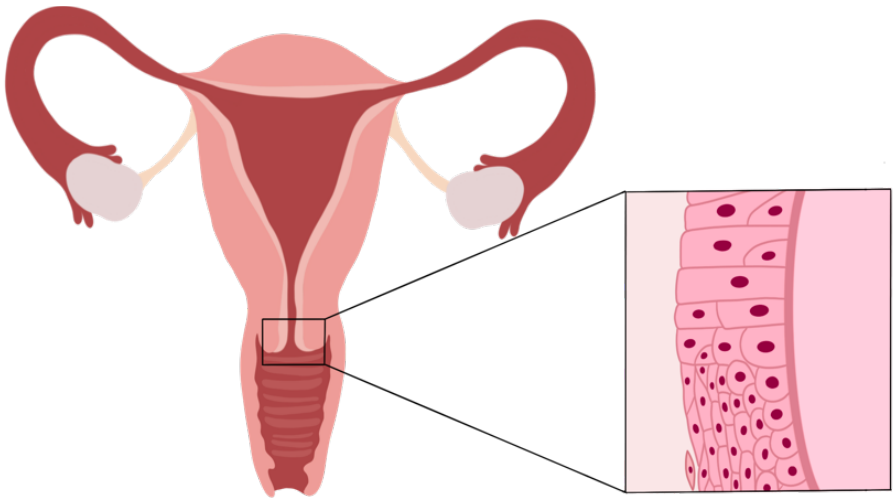
1 Characteristic of the normal vaginal flora
2 Symptom of vaginitis

Section 3 – The Cervix

3.1 – Anatomy and Histology
3.2 – Cervicitis
3.3 – Cervical Cancer
3.4 – Test Yourself

3.1 – Anatomy and Histology

- The cervix is a cylinder-shaped structure that connects the vagina with the uterus.
- It is composed of fibromuscular tissue.
- The cervix can be divided into the *exocervix* and *endocervix*.
- The exocervix is lined by squamous epithelium and the endocervix is lined by columnar epithelium.
- There is an abrupt change from squamous to columnar epithelium called the transformation zone.



3.2 – Cervicitis

- Cervicitis is inflammation of the cervix.
- It is usually caused by an infection with either *Chlamydia trachomatis* or *Neisseria gonorrhea,* or both.

I. Symptoms

- Often asymptomatic
- Abnormal vaginal discharge
- Lower abdominal, and pelvic pain
- During examination, palpation and moving of the cervix can be very painful.

3.3 – Cervical Cancer

- Cervical cancer is one of the most common gynecological cancers after endometrial and ovarian cancer.
- A pap-smear[1] is available in most developed countries and has resulted in a decreased incidence and mortality related to cervical cancer.
- *Cervical intraepithelial neoplasia (CIN),* also known as cervical dysplasia is an abnormal growth of cells in the cervix, which has the potential to become neoplastic.

[1]The pap-smear is a procedure that is used in the screening for of cervical cancer and can detect potentially premalignant lesions in the cervix.

I. Epidemiology

- Most women who develop cervical intraepithelial neoplasia (CIN) have contracted a high-risk strain of HPV during their 20's.
- Because the process of developing dysplasia and eventually invasive carcinoma takes time, symptoms usually present 25-30 years after infection.
- A common symptom of CIN and invasive carcinoma is post-coital bleeding (bleeding after intercourse).

II. Subtypes

- *Squamous cell carcinoma* accounts for 70% of cervical cancers, while *adenocarcinoma* accounts for about 25%.
- Both of these cancers are associated with HPV infection and tend to grow locally without metastasis, until late in the disease.
- They tend to grow into the anterior uterine wall and bladder.
    1. Consequently, a common cause of death and complications in these patients is post-renal failure with hydronephrosis.

III. Etiology

- Human papillomavirus is the main cause of cervical cancer.
- The DNA of HPV can be detected in as many as 99.7% of cervical cancers.
- Therefore, the risk factors for developing cervical cancer are the same risk factors as for contraction of HPV.
    1. Early onset of sexual activity
    2. Multiple sex partners
    3. Sexually transmitted diseases (STD)
    4. Immunosuppression

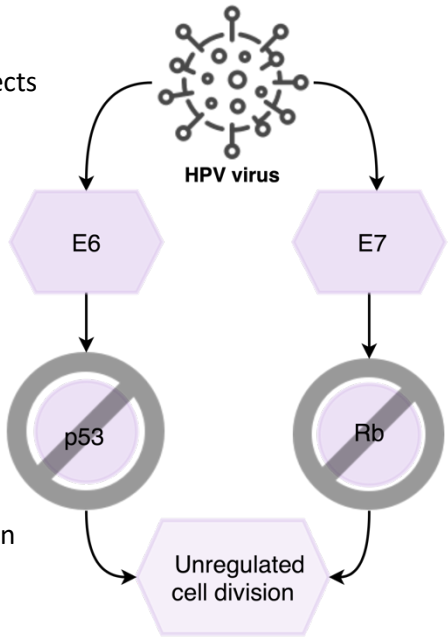
CLINICAL CORRELATION

Cervical cancer and AIDS

- AIDS is characterized by serious and life-threatening diseases seen in HIV-positive people.
- Certain types of diseases are associated with AIDS and therefore called *AIDS-defining illnesses.*
- Cervical cancer is an AIDS-defining illness.

IV. Pathophysiology

- After a woman has contacted HPV, the virus mainly targets and infects the cervix.
- If the viral infection is not cleared by the immune system[1], the premalignant lesion *cervical intraepithelial neoplasia (CIN)* can develop.
- High-risk HPV targets tumor suppressor proteins such as p53 and retinoblastoma protein (Rb).
- The viral production of oncoproteins E6 and E7 destroys the tumor suppressor proteins p53 and Rb, respectively.
- Both p53 and Rb control the cell's progression from the G_2- to the S phase of the cell cycle.
- If these proteins are destroyed, the result is unregulated cell division and ultimately cancer.



[1]The majority of HPV infections are cleared by the immune system.

V. Pathomorphology

- It is important to note the difference between cervical intraepithelial neoplasia and cervical carcinoma
    1. Cervical carcinoma is irreversible
    2. Cervical intraepithelial neoplasia can be reversible.
- To determine the likelihood that CIN will develop into cervical carcinoma, it can be graded from 1-3 according to histological characteristics and the degree of dysplasia present.

Cervical intraepithelial neoplasia			
Stage	Characteristics	Neoplasia risk	Management
CIN 1	Mildly atypical cellular changes that reside within the lower 1/3 of the epithelium Koilocytic[1] change is present	Low risk of progression to malignancy	Observation only, as it can regress spontaneously
CIN 2	A high-grade lesion with moderately atypical cellular changes Resides within the basal 2/3 of the epithelium	50% of patients have spontaneous regression if it is left untreated	Treatment is recommended
CIN 3[2]	A high-grade lesion with severely atypical cellular changes Extends beyond the basal 2/3 of the epithelium	When it invades beyond the epithelium into local tissue it is called cervical carcinoma	Treatment is recommended

[1]Koilocytes are squamous cell that have undergone structural changes after HPV infection

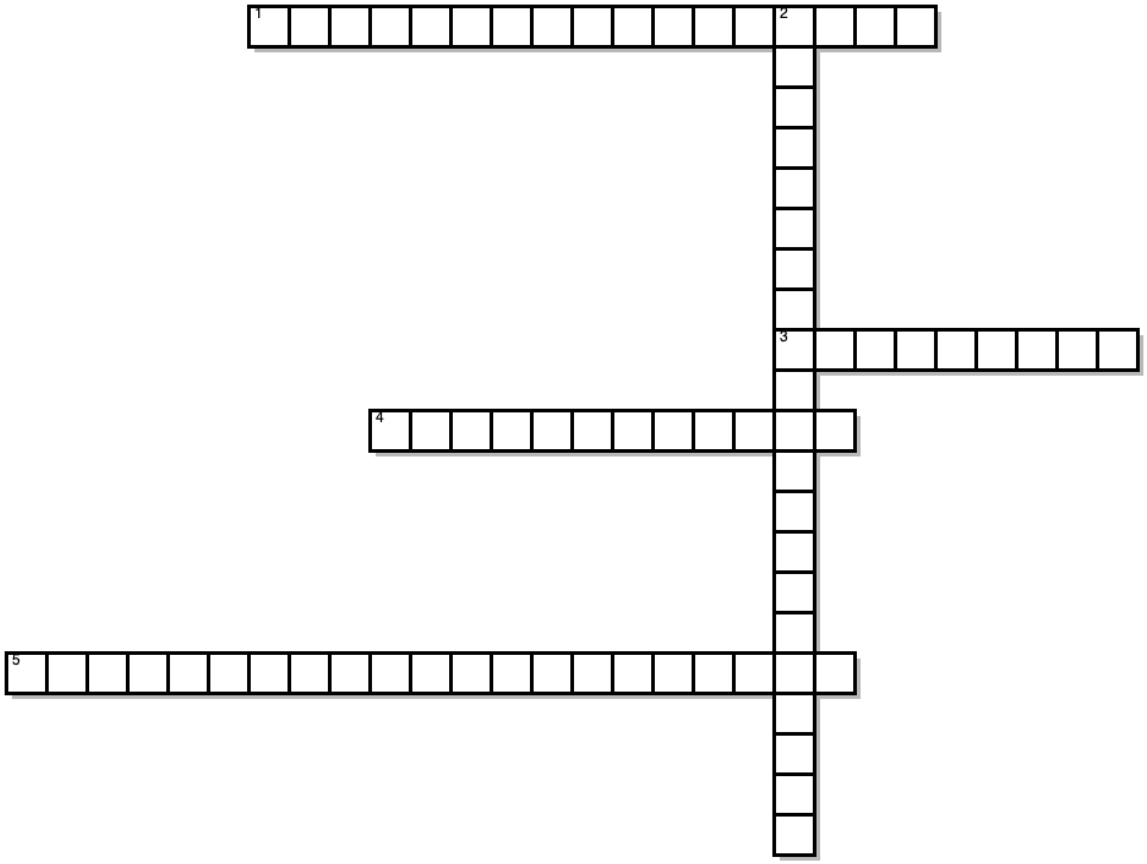
[2]Previously called carcinoma in situ.

Other tumors of the cervix

Nabothian cysts	- Benign lesions; single or multiple - Size: up to 1.5 cm - Caused by obstruction of crypt openings - Resulting in acute and chronic *cervicitis* - Increased risk after subtotal hysterectomy
Endocervical polyp	- Single benign lesion presenting with bleeding or mucoid discharge - Size: up to 1.0 cm - Secondary to chronic inflammation
Microglandular hyperplasia of cervix	- Benign lesion associated with elevated estrogen levels - No association to malignancy
Other cervical adenocarcinomas	Adenosquamous carcinoma of cervix - Same prognosis as other cervical carcinomas - High grade carcinoma Basaloid squamous cell carcinoma of cervix - Aggressive malignancy Glassy cell carcinoma of cervix - Poorly differentiated adenosquamous carcinoma - Aggressive and poor prognosis - Most commonly occurs in the 4th decade of life - Associated with pregnancy and *HPV 16 & 18*
Carcinoid tumors	- Rare - Very aggressive and poor prognosis
Metastasis to cervix[1]	Usually from ovary, breast, colon, stomach or kidney

[1]Extragenital tumors more commonly metastasize to ovaries or vagina

3.4 – Test Yourself



ACROSS

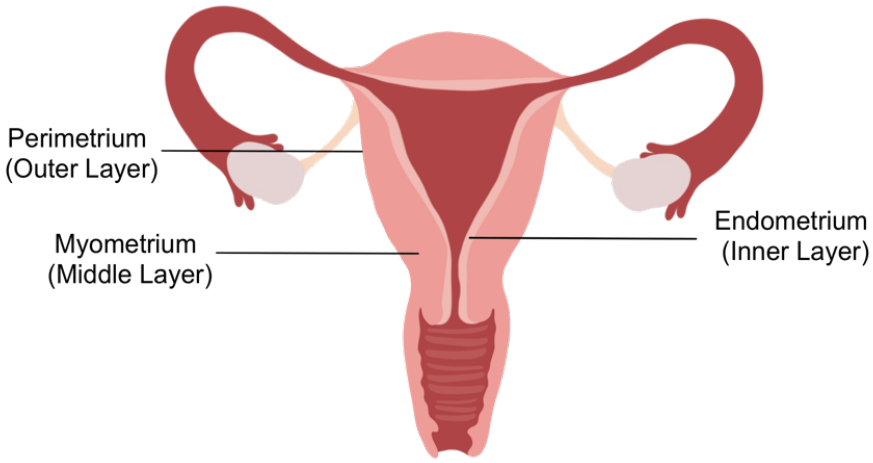
1 Risk factor for developing cervical carcinoma
3 This bacteria can cause cervicitis
4 Cervical carcinoma is
5 Targeted by HPV

DOWN

2 Most common type of cervical cancer

Section 4 – The Uterus

4.1 – Structure
4.2 – Abnormal Uterine Bleeding
4.3 – Amenorrhea
4.4 – Endometriosis
4.5 – Adenomyosis
4.6 – Endometrial Hyperplasia
4.7 – Smooth Muscle Pathology
4.8 – Endometrial Stromal Tumors
4.9 – Endometrial Cancer
4.10 – Salpingitis
4.11 – Test Yourself



4.1 - Structure

- *The endometrium* is the innermost layer of the uterus and consists of a functional layer that sheds during menstruation, and a basal layer which is not shed at any time during the menstrual cycle.
- *The myometrium* lies beneath the endometrium and is made up of smooth muscle. The outer serosal layer of the uterus is known as *the perimetrium*.

4.2 – Abnormal Uterine Bleeding

- Common cause of gynecological consultations.
- Abnormal uterine bleedings can last longer than normal, be increased/decreased in volume or deviate from the regular cycle.
- The most common causes of abnormal uterine bleedings are:
    1. Endometrial polyps usually seen in women < 40 years
    2. Leiomyoma or leiomyosarcoma
    3. Endometrial hyperplasia

DEFINITIONS

Abnormal bleeding

- Dysmenorrhea: Painful menstrual period
- Oligomenorrhea: Time between each menstrual cycle is >35 days
- Polymenorrhagia: Time between each menstrual cycle is <21 days
- Menorrhagia: Menstrual period lasting >7 days
- Metrorrhagia: Irregular bleeding between menses

4.3 – Amenorrhea

- No menstruation
- Amenorrhea can be categorized as *primary* and *secondary amenorrhea*.
- The most common cause of physiological amenorrhea is pregnancy and breastfeeding.

4.3.1 – Primary Amenorrhea

- Primary amenorrhea is defined as the absence of menstruation in:
    1. A 13-year-old who lacks secondary sexual characteristics such as breast development, axillary hair and pubic hair.
    2. A 15-year-old who has developed secondary sexual characteristics.

MNEMONIC

Common causes of primary amenorrhea

XMAS

X – Turner syndrome

M – Müllerian agenesis

A – Androgen insensitivity

S – Swyer syndrome

Causes of primary amenorrhea	
Turner syndrome	The X chromosome in individuals with Turner syndrome is partially or completely missing. Primary hypogonadism with primary amenorrhea is a common feature of the syndrome.
Müllerian agenesis	*Agenesis* is the failure of an organ to develop during embryonal life. The Müllerian ducts are embryonic structures that will develop to form the fallopian tubes, uterus, cervix and upper 1/3 of the vagina. Without these structures, there can be no menstruation.
Androgen insensitivity syndrome	X-linked recessive mutation that generate a defective androgen receptor and therefore insensitivity to androgens. Because androgens play a key role in the hormonal cascade that starts puberty, primary amenorrhea is seen.
Swyer syndrome	A rare syndrome in which the ovaries fail to develop.

4.3.2 – Secondary Amenorrhea

- A woman who began a normal menstrual period during puberty, but lost it at some point, could suffer from secondary amenorrhea.
- It is defined as the absence of menstruation for at least 3 cycles or 3-6 months.
- Secondary amenorrhea can occur with either a low to normal or high FSH.

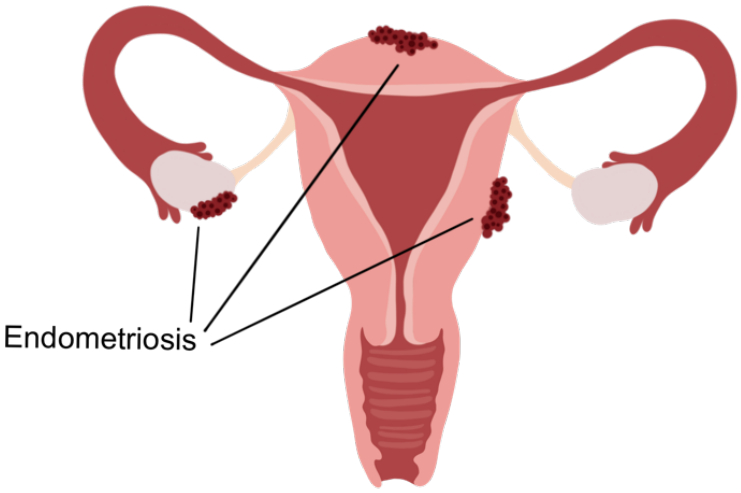
I. Causes

- Functional hypothalamic amenorrhea du to stress or low energy intake.
- Hyperandrogenism such PCOS, where high levels of androgens suppress the release of FSH[1].
- Hyperprolactinemia, which also suppresses the release of FSH.
- Premature menopause

[1]When no FSH is released, the ovarian follicle cannot mature.

4.4 – Endometriosis

- Normally, endometrium is only present inside of the uterus, but in endometriosis, endometrial tissue is present in other locations as well.
- Do not confuse endometriosis with *endometritis*, which is <u>inflammation</u> of the endometrium.
- In endometriosis, endometrial tissue can be found on/in:
    1. Ovaries
    2. Uterine ligaments
    3. Rectovaginal septum
    4. Pelvic peritoneum



I. Response to hormones

- The ectopic endometrial tissue responds to estrogen and progesterone in the same manner as the intrauterine endometrium.
- Remember that at the end of the menstrual cycle, estrogen and progesterone levels decrease and the endometrium is shed as menses.
- <u>This decrease in estrogen and progesterone</u> causes the ectopic endometrial tissue to bleed into the surrounding tissue, which leads to Inflammation with pain and discomfort.

II. Clinical features

- Severe dysmenorrhea
- Pain during sexual intercourse
- Pelvic pain due to intrapelvic bleeding
- Pain during defecation
- Dysuria if the serosa of the bladder is affected
- Menstrual irregularities

<u>CLINICAL CORRELATION</u>

Endometritis

- Common cause of post-partum fever.
- The causative agents are *Gardnerella vaginalis*, *Staphylococcus epidermidis* and group B *Streptococcus.*
- Fever, uterine tenderness and chills are typical symptoms.
- Risk factors include a prolonged delivery, cesarian delivery and multiple cervical examinations.
- Treated with IV antibiotics.

4.5 – Adenomyosis

- *«Adeno»* refers to gland, and *«myos»* to muscle. Adenomyosis is therefore glands within the muscle.
- It is a benign disease characterized by the presence of endometrial glands within the myometrium.
- Incidence of adenomyosis peaks in women age 35-50 years.
- Endometriosis and leiomyomas have been identified as risk factors for development of adenomyosis.

I. Symptoms

- Dysmenorrhea
- Uterine enlargement
- Extensive menstrual bleeding

II. Diagnosis and treatment

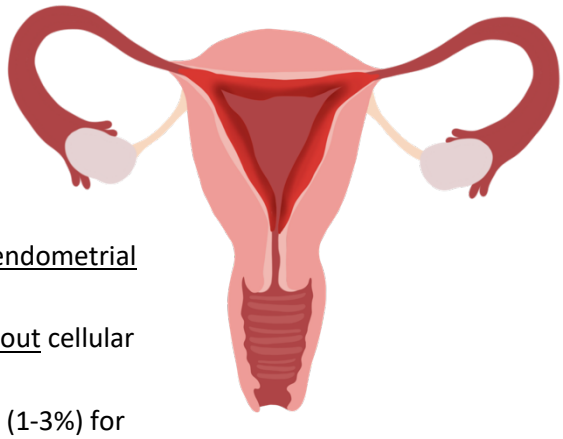
- The diagnosis is clinical, meaning that it is based on the symptomatic presentation of the patient. However, it can be supported by transvaginal ultrasound and MRI findings.
- The treatment consists of combined oral contraceptives, progestin-only contraceptives and NSAIDs for pain relief. Hysterectomy if pharmacotherapy is ineffective.

CLINICAL CORRELATION

Hysterectomy

- The definitive treatment of adenomyosis is a *hysterectomy*
- A hysterectomy is a surgical procedure in which the whole uterus is removed, usually laparoscopically.
- Laparoscopical surgery involves the insertion of short narrow tubes through small incisions in the abdomen, through which longs and narrow instruments can be inserted. It ensures a less invasive approach to surgical procedures.

4.6 – Endometrial Hyperplasia



- Caused by abnormally high and prolonged levels of estrogen stimulation of the endometrium.
- It is typically seen together with low progesterone activity.
- Endometrial hyperplasia is a risk factor for development of endometrial carcinoma.
- Can be categorized into hyperplasia that occurs with or without cellular atypia.
    1. Hyperplasia without cellular atypia carries a low risk (1-3%) for progression into endometrial carcinoma.
    2. Hyperplasia with cellular atypia, also known as *endometrial intraepithelial neoplasia (EIN),* is associated with a much higher risk (20-50%) for progression into endometrial carcinoma. This type of lesions requires careful evaluation, and a total hysterectomy may be the most appropriate treatment.

I. Risk factors

1. *Early menarche* and/or *late menopause*, because they increase the time period in which the endometrium has been exposed to estrogen.
2. *Polycystic ovarian syndrome (PCOS)* due to an increased level of circulating estrogen.

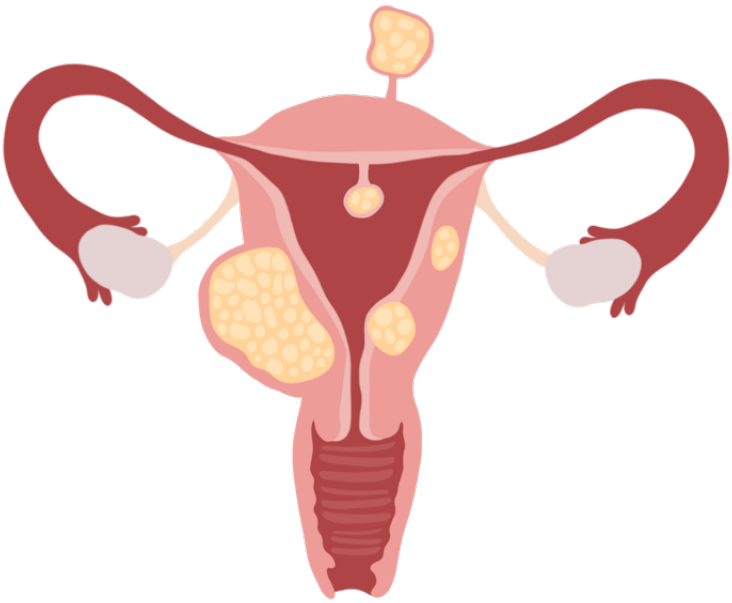
II. Clinical presentation

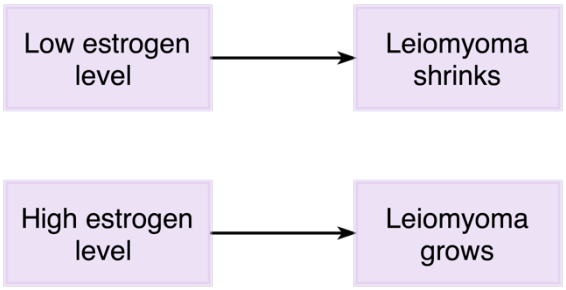
- Abnormal uterine bleedings, typically seen post-menopausal.

4.7 – Smooth Muscle Pathology

I. Leiomyoma

- A tumor of smooth muscle known as *uterine fibroid*.
- It is benign, and the most common pelvic tumor in women.
- It is usually seen in females of reproductive age, and it has a higher incidence is among African American women.
- Leiomyomas respond to estrogen
    1. It will increase in size during pregnancy when estrogen levels are high.
    2. It will decrease in size after menopause when estrogen levels are low.





II. Uterine leiomyosarcoma

- A malignant tumor that arises from the uterine smooth muscle.
- It tends to invade the uterine wall.
- It is important to note that a leiomyosarcomas never arises from a leiomyoma, but *de novo*[1].
- The incidence peaks between 40-60 years of age.

[1] *De novo* means that something arises "from the beginning"

CLINICAL CORRELATION

Leiomyoma and infertility

- Even though there is conflicting data on this subject, it appears that leiomyomas can predispose to infertility.
- The mechanism seems to involve anatomical distortion of the endometrial cavity, diminished blood supply to endometrium and altered uterine contractility.

4.8 – Endometrial Stromal Tumors

- Presents in 5th – 6th decade with vaginal bleeding

Benign	Malignant	
Stromal nodule with pushing nodules	Stromal carcinoma with infiltrating margins	
Well circumscribed Size: up to 10 cm	*Low grade*	*High grade*
	- Slow clinical progression with local recurrence - Metastases to lung results in poor prognosis	- Less common than low grade - Recurrence in pelvis - Metastases to lung - Angiolymphatic invasion - Nuclear atypia - Pleomorphism

4.9 – Endometrial Cancer

I. Overview

- Endometrial adenocarcinoma is the most common *invasive* cancer of the female reproductive tract.
- Postmenopausal women are typically affected, and they typically present with abnormal uterine bleedings.
- A subset of patients can develop a rare cancer known as *uterine papillary serous carcinoma (UPSC)*.

II. Risk factors

- The same risk factor as for endometrial hyperplasia, with <u>increased estrogen exposure</u>
- Obesity and overweight
- Infertility

<u>CLINICAL CORRELATION</u>

Uterine papillary serous carcinoma (UPSC)

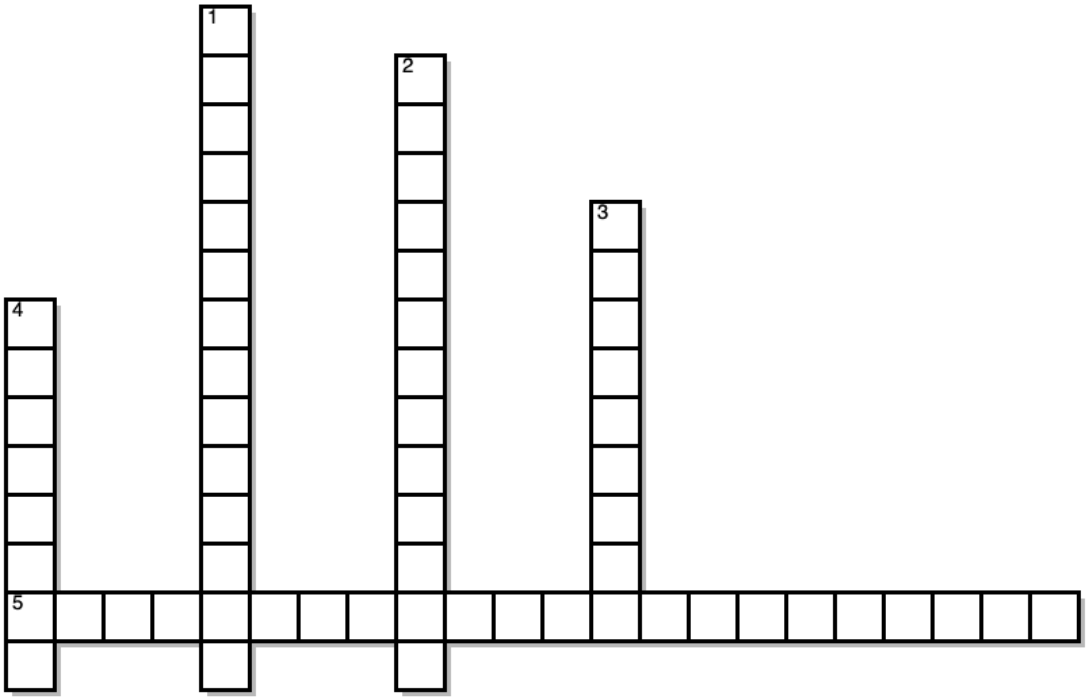
- Is a variant of endometrial cancer.
- UPSC accounts for about 10% of uterine cancers and is associated with a 40% mortality rate.
- It can develop without the presence of endometrial hyperplasia.
- Due to its aggressive nature, primary treatment is surgical removal.

4.10 – Salpingitis

- Inflammation of the fallopian tubes

Acute	- Bacterial infection; sexual transmission - Enlarged, erythematous, edematous tubes - Tubo-ovarian abscess formation is common
Chronic	- Enlarged distorted tube - Blunted, shortened, fibrotic bands - Fused plica produce a *pseudoglandular pattern*

4.11 – Test Yourself



ACROSS

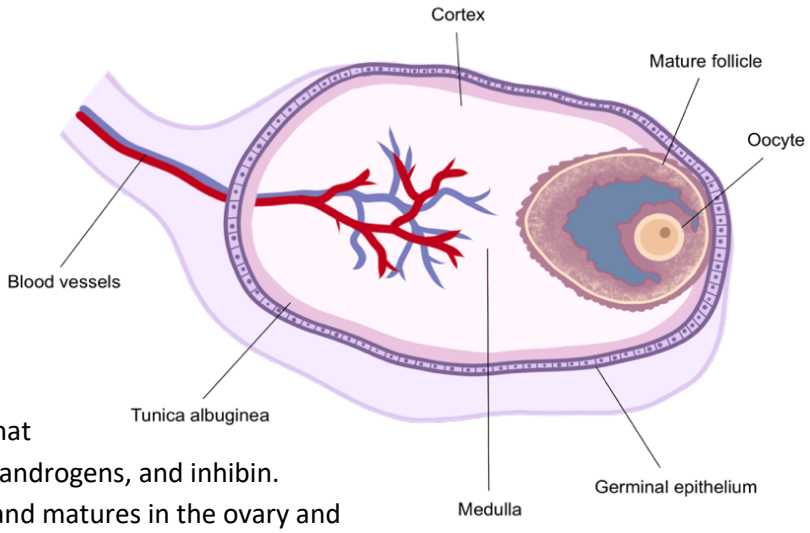
5 Early menarche and late menopause are risk factors for

DOWN

1 A cause of primary amenorrhea
2 Endometrial tissue is found outside the uterus
3 Common cause of physiological secondary amenorrhea
4 Endometrium proliferates in response to this hormone

Section 5 – The Ovaries

5.1 – Overview
5.2 – Polycystic Ovary Syndrome
5.3 – Follicular Cysts
5.4 – Ovarian Tumors
5.5 – Test Yourself



5.1 – Overview

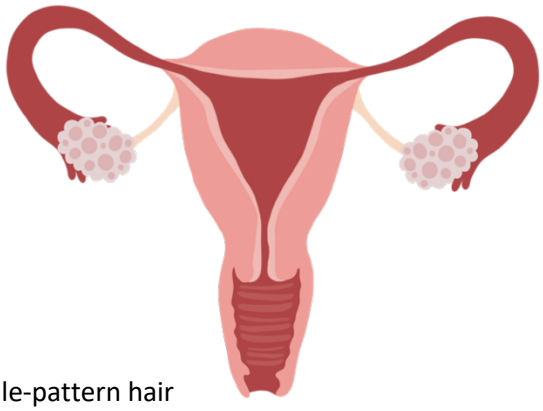
I. Physiology

- The ovary is an endocrine organ that produces estrogen, progesterone androgens, and inhibin.
- The oocyte is the female gamete and matures in the ovary and released during a process known as *ovulation*.

II. Structure

- The ovary is covered by a thick capsule of connective tissue called the *tunica albuginea*.
- Overlying the tunica albuginea is a simple layer of squamous mesothelium which is known as *germinal epithelium*.
- The ovarian follicles are found in the ovarian cortex.
- The medulla of the ovary is a highly vascularized stroma containing blood vessels, lymphatic vessels and nerves.

5.2 – Polycystic Ovary Syndrome (PCOS)



- The most common endocrine disorder in women, affecting about 5-10%

I. Clinical presentation

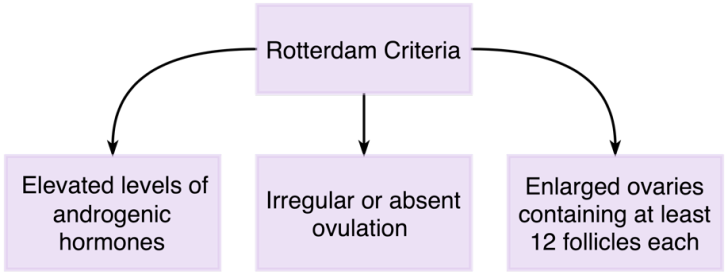
- Overweight or obesity
- Irregular menstruation
- Symptoms of hyperandrogenism such as acne, hirsutism or male-pattern hair loss
- Depression or anxiety disorders

II. Pathophysiology

- Factors such as excess ovarian androgen production, excess insulin, low-grade inflammation are linked to the development of PCOS.
- The exact underlying mechanism is still unknown, but presumably both genetic- and environmental factors can predispose to development of PCOS.
- Obesity is the single most common environmental contributor, and in many cases, there is a positive family history.

III. Diagnosis

- A definitive diagnosis can be made only after excluding other possible conditions.
- Congenital adrenal hyperplasia (CAH) is an inherited disorder that leads to androgen excess and may cause a similar clinical picture.
- The *Rotterdam Criteria* are used to establish the diagnosis, and patients need to fulfill two out of three criteria to be diagnosed with PCOS.



CLINICAL CORRELATION

Infertility and PCOS

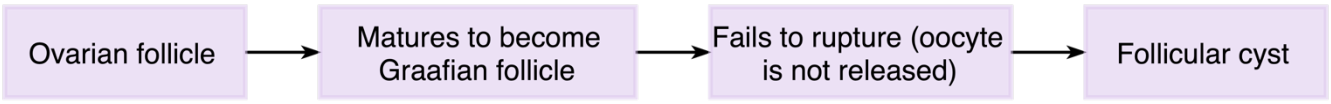
- PCOS is the most common cause of infertility in women.
- Weight loss can reduce serum androgen concentration. Therefore, women who suffer from PCOS who wish to get pregnant are encouraged to lose weight.
- The drug *clomiphene* is typically also given to these women to stimulate ovulation.

5.3 – Follicular Cysts

- Follicular cysts are very common and considered to be *«variants of normal physiology»*.
- They are usually seen in women of reproductive age.

I. Mechanism of formation

- The tertiary ovarian follicle known as the *Graafian follicle*, contains a maturing oocyte.
- The oocyte remains in the tertiary follicle until it is released during ovulation.
- From time to time, the tertiary follicle fails to rupture and release the oocyte.
- In these cases, the follicle continues to grow, and eventually becomes a cyst that can measure up to 7 cm in diameter.



II. Symptoms

- Most follicular cysts are asymptomatic.
- Larger cysts, >5-7 cm in diameter, are more likely to cause symptoms as they can compress the surrounding structures.
- If the cyst ruptures, it can cause intraperitoneal bleeding accompanied by peritoneal symptoms.

III. Significance

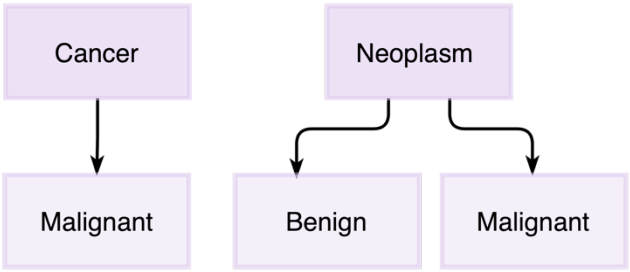
- The granulosa cells lining the follicular cyst produce estrogen, and follicular cysts can therefore cause:
    1. Hyperestrogenism
    2. Endometrial hyperplasia

RECALL

Section 4.6 – Endometrial Hyperplasia

- The endometrial glands grow in response to estrogen stimulation.
- Abnormally high and prolonged levels of estrogen can lead to endometrial hyperplasia.
- Compared with physiological endometrial growth, endometrial hyperplasia has an increased gland-to-stroma ratio >50%.

5.4 – Ovarian Tumors



I. Ovarian cancer

- Accounts for 6% of cancers that occur in women.
- Second most common gynecologic malignancy after endometrial cancer.
- Most common cause of gynecologic cancer death.

II. Presentation

- So-called *«silent killer»* due to its asymptomatic presentation, resulting in late detection.
- Usually presents in women after age of 60.

III. Risk factors

- Nulliparity (a woman who has never been pregnant)
- BRCA1/BRCA2 mutation
- Family history of ovarian cancer

IV. Etiology

- The majority of ovarian malignancies arise from surface epithelial cells.
- The remainder arise from other ovarian cell types.

Ovarian tumors	Subtypes	% of ovarian tumors	Comment
Surface epithelial tumors	Serous tumor Mucinous tumor Endometrioid tumor Clear cell tumor Brenner tumor Cystadenofibroma	60-75%	These tumors can be benign or malignant. 90% of malignant ovarian tumors are of surface epithelial origin. Young women are most commonly affected
Germ cell tumors	Teratoma Dysgerminoma Endogerminal sinus tumor Choriocarcinoma	15-20%	Only 3-5% are malignant. Usually, women <20 years are affected. Cystic teratomas can occur during the reproductive years.
Sex-cord-stroma tumors	Fibroma Granulosa theca-cell tumor Sertoli-Leydig cell tumor	5-10%	2-3% are malignant. These tumors can occur at any age.
Metastasis	☺	5%	Usually from the breasts or GI tract

5.4.1 – Surface Epithelial Tumors

I. Serous epithelial tumors

- Subtypes
    1. *Papillary serous cystadenoma,* which is the most common benign ovarian tumor.
    2. *Papillary serous cystadenocarcinoma*, which is a malignant and frequently bilateral tumor.
- Histopathology
    1. Cystic lesions lined by tall columnar ciliated epithelium.
    2. The cysts are filled with serous fluid.
    3. The epithelium forms papillary structures.
    4. In the tips of the papillae, *psammoma bodies* can be present. These are round collections of calcium.

II. Mucinous epithelial tumors

- Rare occurs before puberty or after menopause.
- This tumor is usually not seen bilaterally.
- A histological examination will reveal cystic lesions filled with mucus and lined by mucous producing cells.
- Can present with *pseudomyxoma peritonei*, which is a rare disease in which cancerous cells secrete mucous that collects within the abdominal cavity.
- Metastasis from a primary gastrointestinal cancer is a common cause of mucinous epithelial tumors.

III. Endometrioid tumor

- Solid tumor composed of endometrial-like glands.
- Can occur bilaterally.
- 20% of endometrioid carcinomas are accompanied by endometrial carcinoma.

IV. Brenner tumor

- An uncommon, solid and usually unilateral tumor that typically occurs in post-menopausal women (5^{th} – 6^{th} decade of life)
- The tumor is encapsulated and contains fibrous stroma. The size can range from a few centimeters to 20 cm in diameter.
    1. Gross pathology: firm yellow/white adenofibroma with cystic areas with yellow-brown fluid
    2. Microscopic pathology: Epithelial component consists of sharply demarcated *nests of urothelial-like cells*
- Slow growing and usually benign, about 5% are malignant.
- Treatments consists of surgical removal of the tumor, and the long-term prognosis is excellent.
- Associated with uterine bleeding and endometrial hyperplasia, mucinous cystadenoma, struma ovarii, and urothelial carcinoma of the bladder

5.4.2 – Germ Cell Tumors

I. Mature teratoma

- Also called *dermoid cyst* and is the most common germinal cell tumor.
- It is a cystic neoplasm made of up cells from two or three embryonic layers (*endoderm*, *ectoderm* or *mesoderm*)
- The tumor can contain various tissues such as skin, hair, and bones.
- It is usually benign, but about 1% of tumors can undergo malignant transformation.
- About 10-15% are found bilaterally.
- Some mature teratomas contain thyroid tissue (*struma ovarii*) which secrete T3 and T4, leading to *secondary hyperthyroidism*.

II. Immature malignant teratoma

- Usually seen in prepubertal adolescent and young women.
- Can contain a mixture of adult and embryonic tissues such as cartilage, bone, muscle and nerves.

III. Dysgerminoma

- Morphologically analogous to a *testicular seminoma* in males.
- It consists of large cells with a clear cytoplasm and well-defined borders.
- Malignant, but it responds well to radiotherapy.
- Cases of dysgerminoma have been reported in girls with Turner syndrome**.**

IV. Endodermal sinus tumor

- Also called *yolk sack tumor* as it is histologically similar to the mesenchyma of the primitive yolk sack.
- It is the most common ovarian tumor in girls less than 5 years of age.
- It has a low incidence but is the second most common tumor of germ cell origin.
- Rich in α- fetoprotein.

V. Ovarian choriocarcinoma

- Do not confuse ovarian choriocarcinoma with the gestational tumor choriocarcinoma.
- Made up of placenta-like tissue.
- Usually coincide with other germ cell tumors.
- Produces beta-hCG (human chorionic gonadotropin), which can be detected by a pregnancy test.
- By the time of diagnosis, metastasis to other organs is usually seen.

CLINICAL CORRELATION

Turner Syndrome

- Turner syndrome is one of the most common chromosomal anomalies in females.
- It results from the complete or partial loss of the X chromosome.
- These girls present with a short stature, widely spaced nipples, and a webbed neck.
- Girls with Turner syndrome almost always have primary ovarian insufficiency, and many also have cardiac anomalies such as aortic valve disease and coarctation of the aorta.

5.4.3 – Sex Cord-Stromal Tumors

I. Granulosa-Theca cell tumor

- A potentially malignant tumor composed of a mixture of granulosa and theca cells.
- May produce large amounts of estrogen, which can lead to:
    1. Precocious sexual development
    2. Endometrial hyperplasia or endometrial carcinoma in post-menopausal women.
- Characterized by *Call-Exner bodies*, which are small follicles containing eosinophilic materials.

II. Sertoli-Leydig cell tumor

- Also called *androblastoma.*
- Secretes androgens, which can lead to:
    1. Inhibition of normal sexual development in children.
    2. Virilization
- Exhibit tubules composed of Sertoli cells or Leydig cells interspersed with stroma.

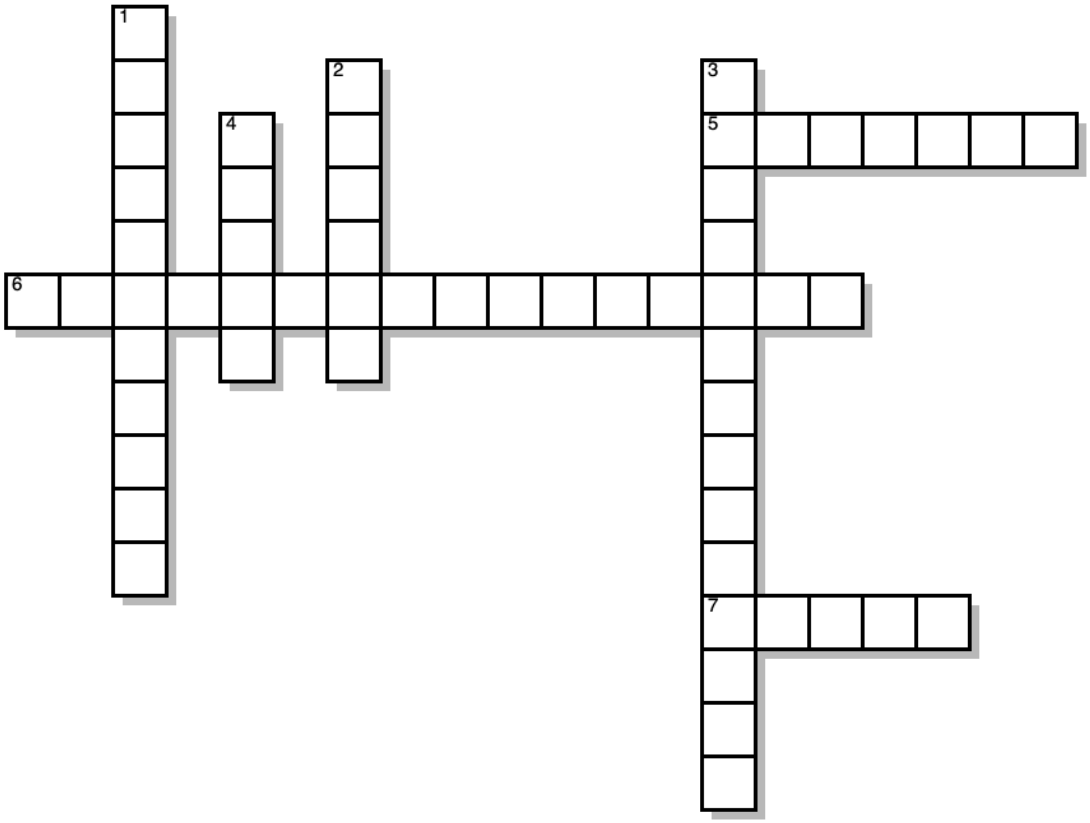
5.4.4 – Metastasis to the Ovaries

- Krukenberg tumor**:** Primary cancer of the gastrointestinal tract or breast that usually metastasizes to both ovaries.

Other tumors of the ovaries

Small cell carcinoma of the ovary	<u>Hypercalcemic type</u> - Bilateral, diploid, malignant tumor associated with hypercalcemia - Affects young women, age 9-43 - Poor prognosis due to metastases - Not associated with high levels of estrogen - Rare and highly malignant

5.5 – Test Yourself



ACROSS

5 Most common environmental contributor to the development of PCOS
6 Possible complication of a follicular cyst
7 USG can reveal this in a young woman with hirsutism and obesity

DOWN

1 Risk factor for developing an ovarian tumor
2 Ovarian metastasis usually originate from this primary site
3 Variants of normal physiology
4 Endometrium found here causes severe pain before and during menstruation

Section 6 – The Breast

6.1 – Benign Breast Conditions
6.2 – Breast Carcinoma
6.3 – Test Yourself

6.1 – Benign Breast Conditions

I. Fibroadenoma

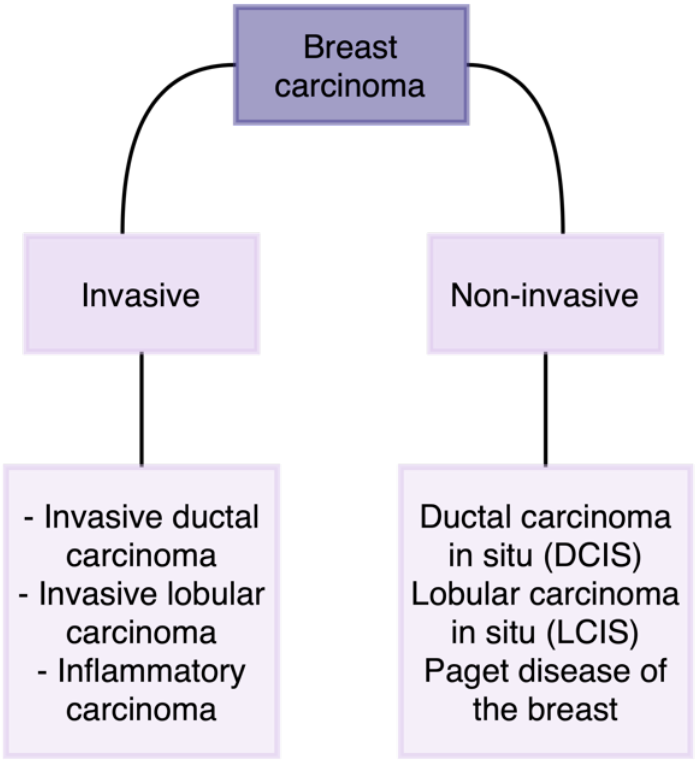
- Most common benign tumor of the breast.
- Composed of fibrous and glandular tissue.
- It frequently occurs in the upper outer quadrant of the breast.
- Most fibroadenomas do not increase the overall risk of developing breast cancer.

II. Intraductal papilloma

- Benign tumor that can arise as a solitary lesion or as multiple lesions.
- It is usually located in the lactiferous sinus and can harbor areas of atypical cells and/or ductal carcinoma in situ (DCIS).
- More than 80% of women with an intraductal papilloma will present with serous or bloody nipple discharge.
- Tumor excision should be considered if there is evidence of DCIS or complaints of bloody nipple discharge.

6.2 – Breast Carcinoma

- Breast carcinoma is the most common malignancy in women, after certain types of skin cancers.
- Breast cancer is the second most common cause of mortality in women due to cancer.
- It usually affects post-menopausal women, and the mean age of incidence is 64 years.
- Breast carcinoma develops before the age of 25, except in familial syndromes.
- Since the introduction of *mammography screening* in the 1980's, the mortality due to breast carcinoma has dropped from 30% to less than 20%.
- Most commonly located in the upper-outer quadrant of the breast.



I. Pathomorphology

- Axillary lymph node involvement is the single most important prognostic factor.
- It arises from the epithelium of the mammary ducts or lobular glands.
- Classified according to whether or not there is invasion beyond the basal membrane. Invasive carcinoma has invaded beyond the basal membrane, whereas carcinoma in situ has not.

CLINICAL CORRELATION

Male breast cancer

- Female to male ratio of 125 to 1
- Associated with a BRCA2 mutation
- Mostly ductal carcinoma

II. Noninvasive carcinomas

- Lobular carcinoma in situ (LCIS)
    1. LCIS arises from the lobules of the terminal ducts of the breast.
    2. It is usually discovered with a breast biopsy, performed for another reason.
    3. Typically, asymptomatic, but patients may present with a small lump in the breast.
    4. Although it is not classified as breast cancer, women with LCIS have an increased risk of developing invasive breast cancer.
    5. The only treatment required is surgical removal of the lesion.
- Ductal carcinoma in situ (DCIS)
    1. DCIS is considered the earliest form of breast cancer.
    2. More than 90% are detected with mammography.
    3. The final diagnosis is made with a biopsy of the lesion, and the morphological appearances can vary greatly.
    4. Breast-conserving therapy with radiation or a mastectomy (removal of all breast tissue) are the treatment options for DCIS.
    5. The subtype *comedocarcinoma* is characterized by extensive central necrosis.
- Paget Disease of the breast
    1. Accounts for only 1-3% of cases of female breast cancer.
    2. It is caused by the extension of DCIS through the lactiferous sinus and into the skin of the nipple. This causes crusting and exudate over the nipple and areola, occasionally with bloody nipple discharge.

III. Invasive carcinomas

- Invasive ductal carcinoma:
    1. Includes the carcinomas that do not fit into any other category of invasive breast carcinoma.
    2. Accounts for about 70-80% of invasive carcinomas.
    3. Usually associated with ductal carcinoma in situ (DCIS).
    4. 65% are positive for estrogen receptors (ER), and 20% are positive for human epidermal growth factor receptor 2 (HER2).
- Invasive lobular carcinoma:
    1. Account for 10-15% of all breast carcinomas.
    2. The pattern of metastasis is unique, because it tends to spread to the cerebrospinal fluid, GI tract, ovaries, uterus and bone marrow.
- Inflammatory carcinoma:
    1. Usually presents with a swollen erythematous breast, and a palpable mass.

IV. Genetics and hormonal receptors

- A mutation in the BRCA1/BRCA2 genes are strong hereditary risk factors for developing breast carcinoma.
- Additionally, mutations in the p53 tumor suppressor gene are also associated with a high- to moderate-risk of developing breast carcinoma.
- Estrogen receptors (ER) and progesterone receptors (PR) are overexpressed in most malignant breast tissue.

V. Risk factors

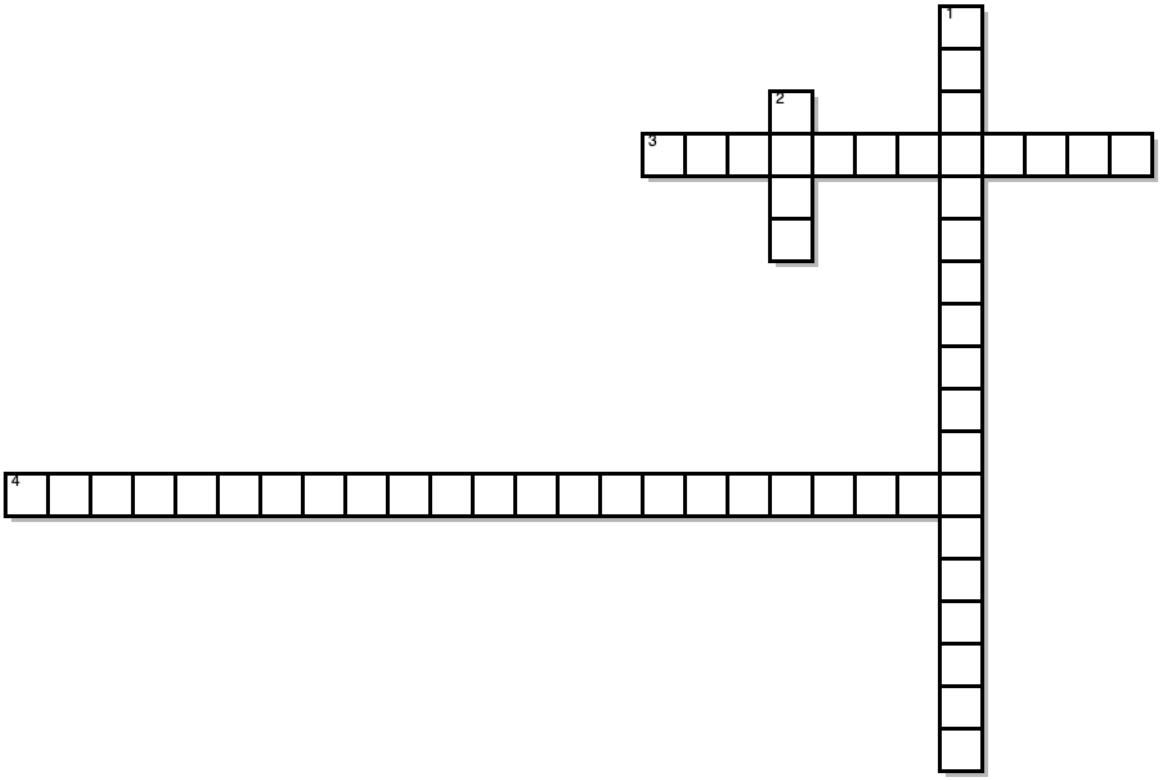
- Increased exposure to estrogen as in early menarche and late menopause
- Advanced maternal age >30 years
- Obesity
- Nulliparity
- Non-breastfeeding women
- BRCA mutations

CLINICAL CORRELATION

BRCA1/BRCA2 mutation

- BRCA1/2 are genes that encode for tumor suppressor proteins.
- Normally, these proteins repair damaged DNA.
- A mutation in either of these genes is associated with an increased risk of breast, ovarian and other cancers.
- These mutations can be inherited in autosomal dominant pattern.

6.3 – Test Yourself



ACROSS

3 Most common benign tumor of the breast
4 Most common type of invasive breast carcinoma

DOWN

1 Invasive lobular carcinoma can spread to
2 Two pair of genes that impact a person's chance of developing breast cancer

Section 7 – Female Infertility

7.1 – Overview
7.2 – Ovarian Causes
7.3 – Tubal and Pelvic Causes
7.4 – Test Yourself

7.1 – Overview

- Infertility is defined as the inability of two people of the opposite sex together for 12 months despite regular unprotected vaginal intercourse (2+ times a week)
    1. 1/3 of causes from male only
    2. 1/3 of cause from female only
    3. 1/3 of cause from both partners.
    4. Affects up to 15% of sexually active couples.

I. Epidemiology

- Infertility affects approximately 10-15% of couples during their reproductive age.
- In women, *primary ovarian insufficiency* is the most common cause of infertility.

Etiology	% of cases	Example
Primary ovarian insufficiency	30%	-
Sexual dysfunction	10%	Sexual arousal disorders or pelvic pain disorder
Diminished ovarian reserves	10%	-
Uterine anomalies	5%	Congenital anomalies of the uterus
Cervical anomalies	5%	Congenital anomalies of the cervix

7.2 – Ovarian Causes

- Ovarian insufficiency is the cause of female infertility in 30% of cases.

I. Primary ovarian insufficiency

- Also referred to as *hypergonadotropic hypogonadism* and is a causes secondary amenorrhea.
- Idiopathic in 90% of cases.
- Lab values show high levels of FSH and decreased estrogen.
- Is sometimes associated with autoimmune disease such as Hashimoto's thyroiditis, Addison's disease and diabetes mellitus type 1.
- The pathophysiology involves depletion or dysfunction of the ovarian follicles, which causes estrogen levels to fall markedly.
- Symptoms mimic those associated with menopause, such as vaginal dryness, night sweats, hot flashes, pain during sexual intercourse and irritability.

RECALL

Section 4.3 – Amenorrhea
Primary ovarian insufficiency is one of the causes of secondary amenorrhea.

II. Secondary ovarian insufficiency

- The ovaries are normal, but due to some pathology of either the pituitary gland or the hypothalamus, they are malfunctioning.
- Causes of secondary ovarian insufficiency are include neoplasm, trauma, infection, eating disorders and even drugs abuse. Each of these can lead to disturbances in the CNS which can decreases secretion of gonadotropic hormones.
- Lab values show decreased pituitary hormones like FSH and LH, which ultimately leads to decreased estrogen levels.

7.3 – Tubal and Pelvic Causes

I. Overview

- Obstruction of the fallopian tubes prevents the passage of sperm and can inhibit fertilization.
- *Pelvic inflammatory disease (PID)* can lead to scarring and adhesion of the fallopian tubes, and account for about 30% of cases of female infertility.

7.3.1 – Pelvic Inflammatory Disease

I. Overview

- Pelvic inflammatory disease is caused by a bacterial infection that spreads from the cervix to the fallopian tubes, uterus, ovaries and surrounding tissue.
- It is a complication of an untreated sexually transmitted infection (STI). *Neisseria gonorrhea* or *chlamydia trachomatis* are the most common responsible pathogens.
- In a minority of cases, other organisms such as anaerobes, aerobic gram-negative rods, streptococci and mycoplasma genitalium cause PID.
- PID is a clinical diagnosis.

CLINICAL CORRELATION

Ectopic pregnancy

- Is an extrauterine pregnancy that usually occurs in the fallopian tube.
- The most common clinical presentation is first-trimester vaginal bleeding and/or abdominal pain.
- Treatment of choice is with the folate antagonist *methotrexate*.
- If the patient is hemodynamically unstable surgical intervention is usually required.

II. Pathogenesis

- Infection of the uterus and fallopian tubes causes inflammation.
- Post-infectious scarring of the fallopian tubes increases the risk of developing an ectopic pregnancy.

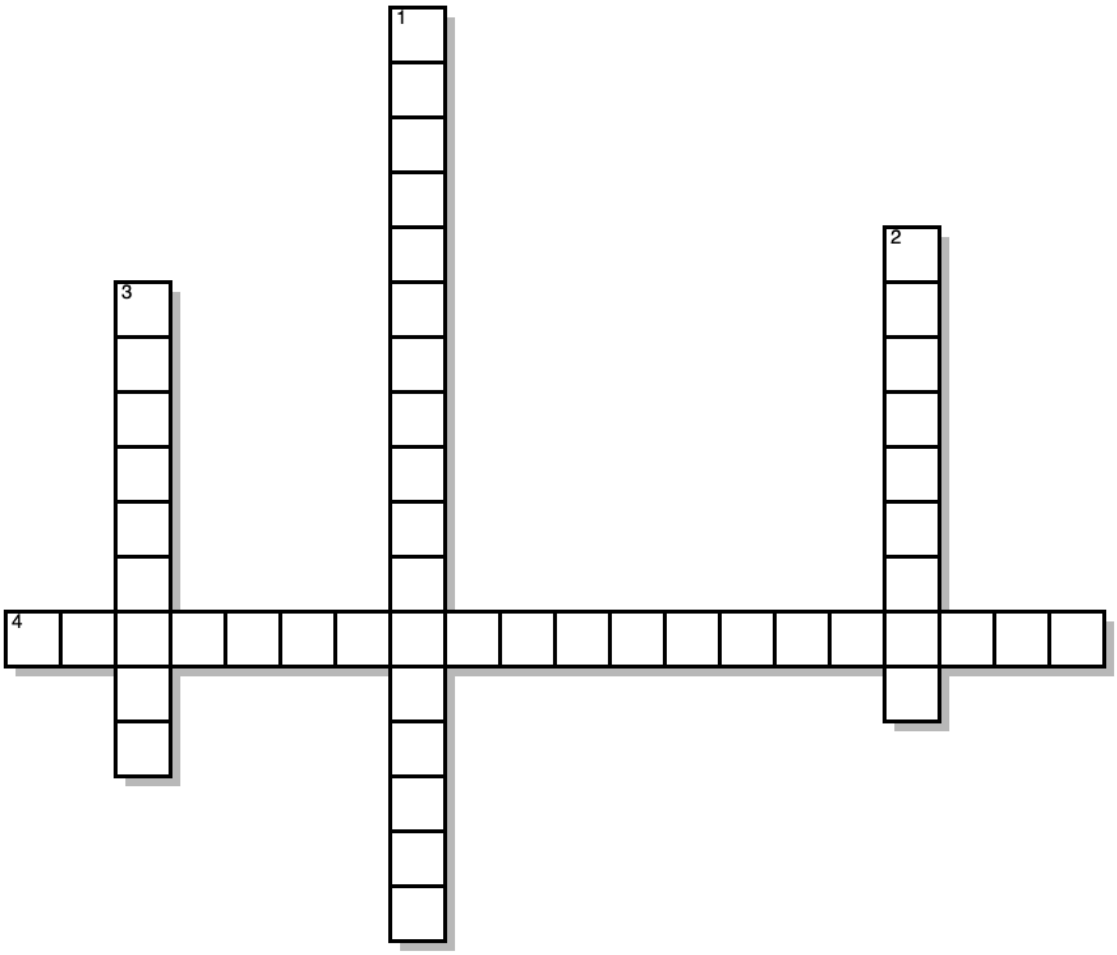
III. Symptoms

- Lower abdominal pain, abnormal vaginal discharge, nausea and vomiting, menorrhagia and metrorrhagia.
- Many women experience only mild symptoms, and some are even completely asymptomatic.

VI. Treatment

- Antibiotics are the treatment of choice when PID is suspected.
- If the patient is unable to take oral antibiotics, she should be hospitalized for IV antibiotics therapy.
    1. Severe clinical illness and pregnancy are indications for in-hospital treatment
- A combination regime consisting of a cephalosporin, together with a tetracycline and metronidazole is usually preferred

7.4 – Test Yourself



ACROSS

4 Most common cause of secondary amenorrhea

DOWN

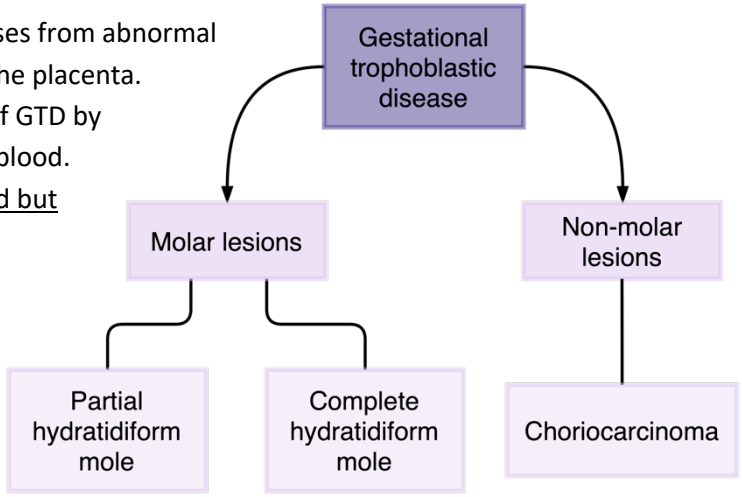
1 Can be seen in women with primary ovarian insufficiency
2 A pathogen that can cause pelvic inflammatory disease
3 Structure that releases FSH and LH

Section 8 – Gestational Pathologies

8.1 – Gestational Trophoblastic Disease
8.2 – Choriocarcinoma
8.3 – Hydatidiform Mole
8.4 – Test Yourself

- Gestational = Related to pregnancy

8.1 – Gestational Trophoblastic Disease



- *Gestational trophoblastic disease (GTD)* arises from abnormal proliferation of fetal trophoblastic cells in the placenta.
- It is possible to monitor the development of GTD by observing the changes of hCG levels in the blood.
- Typically has an early hematogenous spread but responds excellently to chemotherapy.

8.2 – Choriocarcinoma

- Highly malignant epithelial tumor.
- Responds excellently to chemotherapy, and cure rates are from 90-100%.
- Can arise from any kind of trophoblastic tissue:
    1. Hydatidiform mole (50%)
    2. Miscarriage or ectopic pregnancy (25%)
    3. Normal term pregnancy (25%)

I. Histopathology

- Extensive necrosis, hemorrhage and vascular invasion.
- It tends to metastasize early, and usually spreads to the lungs, liver, brain, pelvis, spleen and intestines.

II. Symptoms

- Vaginal bleeding
- Depending on the site of metastasis, cough, dyspnea, headache and dizziness can also be present.

8.3 – Hydatidiform Mole

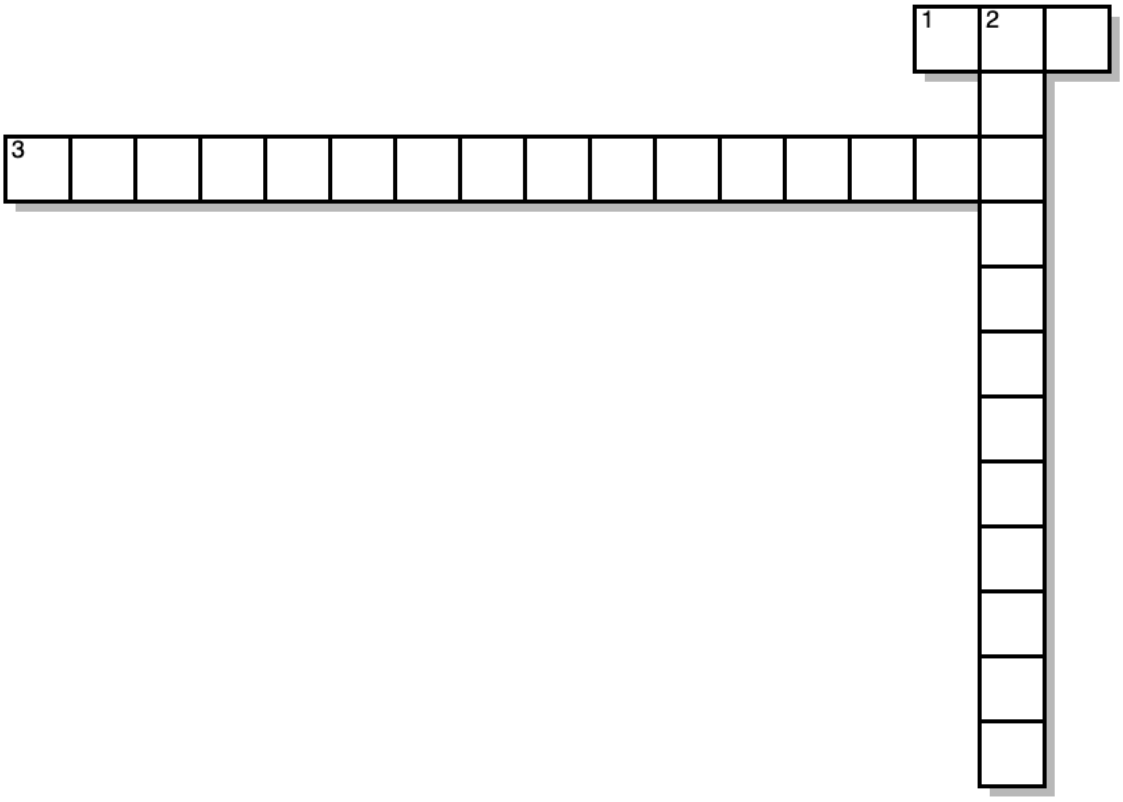
- A premalignant lesion also known as a *molar pregnancy*.
- It is the most common manifestation of gestational trophoblastic disease.
- Molar pregnancies have the potential to become *gestational trophoblastic neoplasia*.
- It can be divided into two subtypes depending on chromosomal pattern, histopathology, clinical presentation and outcome:
    1. Complete mole
    2. Partial mole

I. Symptoms

- Symptoms often start during the fourth or fifth month of pregnancy
- Vaginal bleeding
- Missed menstrual period, nausea and pelvic discomfort
- Presence of hCG in blood

Subtypes	Karyotype	Fetal or embryonic tissue	hCG level	Risk of gestational trophoblastic neoplasia
Complete Mole	46 XX or XY All chromosomes are paternal	Absent	Highly elevated	15-20%
Partial Mole	69 XXY or XYY The extra set of chromosomes are paternal	Present	Slightly elevated	1-5%

8.4 – Test Yourself



ACROSS

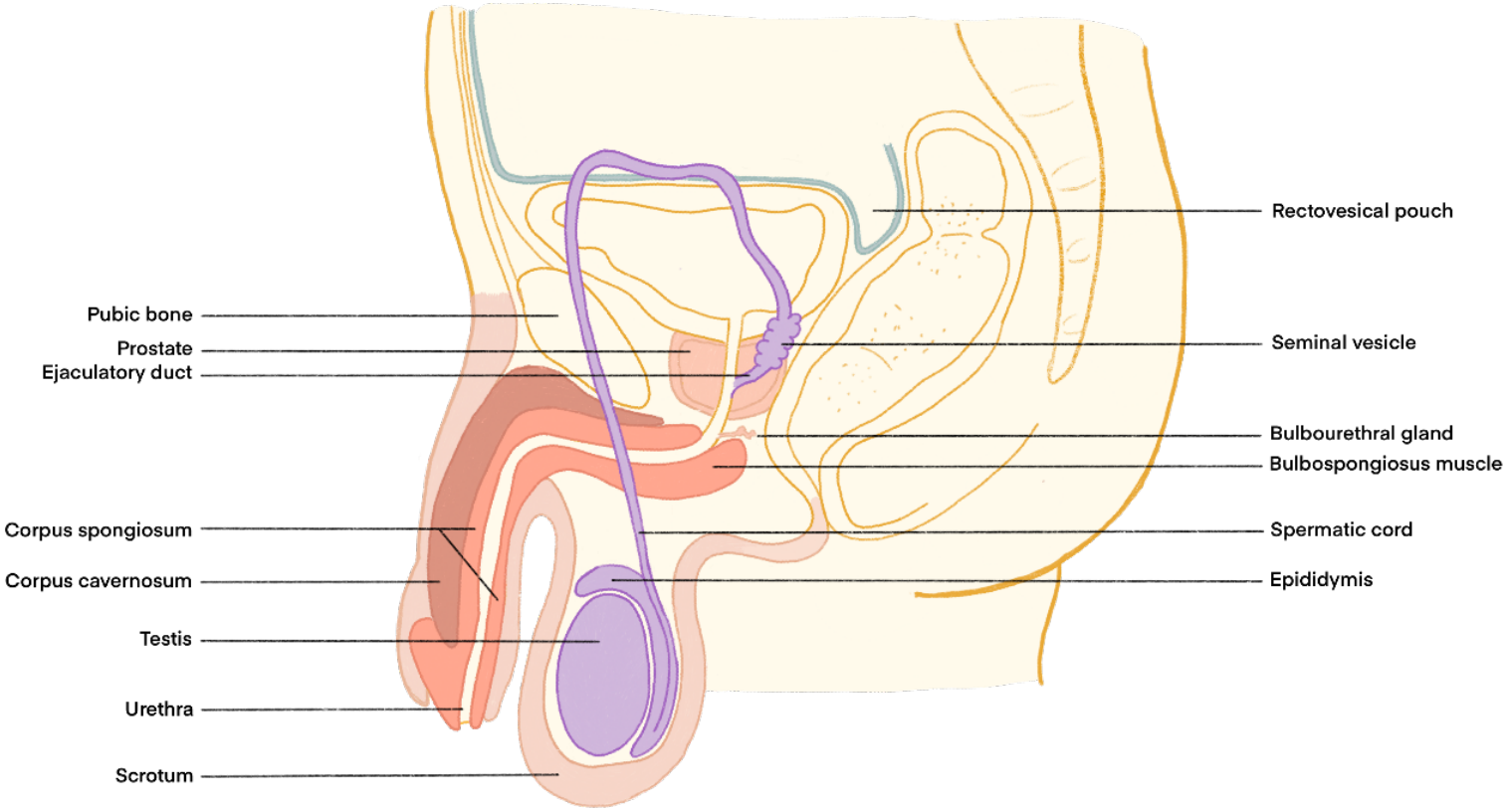
1 Lab parameter used to monitor disease progression
3 Most common manifestation of GTD

DOWN

2 GTD is treated with

PART 2 – MALE REPRODUCTIVE SYSTEM

Review of male reproductive anatomy

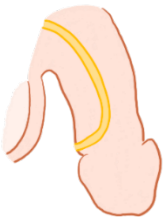


Section 1 – The Penis

1.1 – Malformation of Urethral Canal
1.2 – Balanitis
1.3 – Cysts
1.4 – Erectile Problems
1.5 – Penile Tumors
1.6 – Test Yourself

1.1 – Malformations of the Urethral Canal

- Congenital disease
    1. Congenital anomalies are problems occurring during development in utero.
- The urethral opening is inappropriately located on the penile shaft.
    1. Can be located anywhere along the penile shaft.
- Associated with UTIs, sterility if severely displaced.
- Treated surgically to prevent the above complications.

Feature	Epispadias	Hypospadias[1]
Location	Top of penis	Bottom of penis
Association	Bladder exstrophy[2]	Inguinal hernia, cryptorchidism[3], chordee[4]
Memory aid	"epi" means above	"hypo" means below
Appearance		

[1] Hypospadias is more common.
[2]The bladder wall fails to form properly, hence the bladder is outside of the abdomen.
[3]Cryptorchidism refers to a failure of the testicles to descend into the scrotum before birth. Treated if failure to descend persists until 6-12 months after delivery.
[4]Chordee is an abnormal curvature of the penis.

CLINICAL CORRELATION

Urethral polyps
- Benign, NOT precancerous
- Present in 3rd-4th decade with blood in the urine or sperm
- Made up of cells originating from the prostate.
- Tall, columnar cells.

1.2 – Balanitis

- Inflammation of glans penis.
- May or may not be infectious.
- Usually leads to balanoposthitis, unless circumcised.
- When both chronic and noninfectious, it is referred to as *balanitis xerotica obliterans* (previously called *lichen sclerosus et atrophicus*)
    1. Male equivalent of lichen sclerosus of vulva.
    2. Most commonly affects older males, often with autoimmune conditions and HPV infection.
    3. Associated with an increased risk of cancer – especially a lower grade squamous cell carcinoma in the glans penis and prepuce.
    4. Affects the prepuce, coronal sulcus, glans penis, and even urethra when advanced. This can lead to narrowing of the urethral meatus and phimosis (inability to retract foreskin)
    5. Epithelial dysplastic changes visible.
    6. Circumcision is used as treatment, but it may still reoccur.

CLINICAL CORRELATION

Smegma

- Accumulation of oils and dead skin cells
- Occurs under the foreskin in males.
- Localized by the clitoris and labia minora.

DEFINITIONS

Penile inflammation

Posthitis = Inflammation of the prepuce (foreskin)

Balanoposthitis = Inflammation of the glans penis and prepuce and can lead to the formation of smegma.

1.3 – Cysts

	Epithelial inclusion cysts[1]	Mucoid cysts	Median raphe cysts[2]	Epidermoid cysts[3]
Location	Penile shaft	Prepuce and glans penis	Bottom of head of penis	In sebaceous glands
Size	1mm to 1cm	2mm to 2cm	☺	☺
Composition	Stratified squamous epithelium	Stratified columnar epithelium	Pseudostratified columnar epithelium	Keratin

[1] Most common

[2] Developmental defect . Generally not noticed until adolescence/adulthood once they have grown enough to cause local inflammation.

[3] Usually harmless. Painful if large, and should then be removed

CLINICAL CORRELATION

Fordyce spots

- Naturally occurring small white bumps in oral cavity or by genitals
- Affect 70-80% of adults
- Appear during puberty from increasing hormone stimulation of sebaceous glands
- Generally not problematic
- Important differential diagnosis for cysts and STD lesions

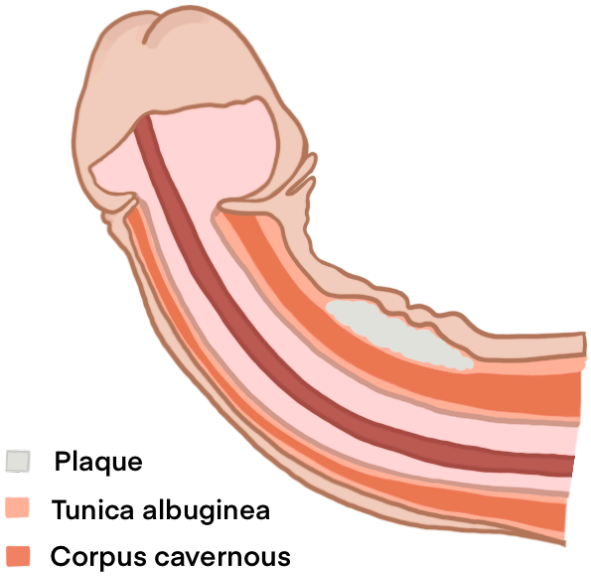
1.4 – Erectile Problems

CLINICAL CORRELATION

Dupuytren contracture
- 1+ fingers are permanently flexed
- Seen in 10% of Peyronie's patients

I. Peyronie disease

- Abnormal curvature of penis.
- May cause erectile dysfunction, pain during erection, difficulties having intercourse, shortening of penis, and loss of girth.
- Primarily affects men over 40.
- Caused by growth of fibrous scar tissue in soft tissue of the penis, particularly the tunica albuginea.
    1. The tunica albuginea is the sheath surrounding each corpora cavernosa.
    2. Both corpora cavernosa accumulate blood like sponges to form and maintain an erection.
- One third will resolve spontaneously. The rest will require treatment with steroid injection or surgery.



II. Priapism

- Unwanted, painful erection lasting > 4 hours.
- May be caused by medication (e.g: sildenafil), spider bites, or sickle cell disease
- Medical emergency due to risk of ischemia.
- Treated with drainage, penile phenylephrine injection, or surgical decompression

III. Penile fracture

- This is a rupture of the corpora cavernosa occurring during erection.
- Generally occurs during intercourse, most associated position is cowgirl.

1.5 – Penile Tumors

1.5.1 – Benign

I. Condyloma acuminatum

- Red papillary outgrowth ranging from 1-5 mm in diameter, may be sessile or pedunculated.
- Most commonly grow by coronal sulcus or inner prepuce.
- Microscopically presents with branching papillae covered by organized, hyperplastic stratified squamous epithelium. Hyperkeratosis and koilocytosis are common.
    1. The thickened epithelium is referred to as acanthosis.
    2. Koilocytosis is classic in HPV infection and refers to the epithelial cells undergoing structural changes and forming vacuoles.
- Associated with HPV infection, particularly types 6 and 11
- Treated with excision, may recur but rarely malignant

CLINICAL CORRELATION

Skin lesions

- Macule: flat, discolored area ≤ 1 cm in diameter.
- Patch: flat, discolored area > 1 cm
- Papule: raised skin lesion ≤ 1 cm
- Nodule: raised lesion ≥ 1cm in diameter and depth.

1.5.2 – Malignant

- Slow growing
- Regional metastasis: Inguinal and iliac lymph nodes

I. Carcinoma in situ (CIS)

- Associated with HPV, especially type 16.
- Precursor lesions to full carcinoma

Feature	Bowen disease	Bowenoid papulosis	Erythroplasia of Queyrat
Location	Shaft or scrotum	Shaft	Glans penis, prepuce
Presentation	Leukoplakia	Multiple reddish papules	Erythroplakia
Age	30-40s	20-30s	40-50s
Progression to carcinoma	5-10%	Extremely rare	5-10%
Association with internal cancer	33%	None	10%

I. Squamous cell carcinoma

- *What?* Malignant, invasive proliferation of squamous cells of penile skin.
    1. Epithelial thickening on glans penis or the inner surface of the prepuce.
- *With?* HPV, tobacco, radiation and PUVA therapy.
- *Who?* Primarily affects uncircumcised men due to difficulty practicing proper hygiene

CLINICAL CORRELATION

PUVA therapy

- **P**soralen and **u**ltra**v**iolet **A**
- UV light treatment for skin diseases.
- Used for psoriasis, eczema, vitiligo, graft-vs-host-disease, and cutaneous T-cell lymphoma

- Progresses to ulcero-infiltrative or exophytic growth that destroys the penile tip and/or shaft.
    1. Exophytic means growing out past the surface epithelium.
- Variants include
    1. Verrucous carcinoma: grows slowly but quickly involves bones
    2. Papillary: looks like a wart, deep infiltration
    3. Basaloid: deep penetration, poor differentiation
    4. Adeno-squamous: deeply invasive
    5. Sarcomatoid (spindle-cell): forms masses with polyps

1.6 – Test Yourself

1) Assign the below to either epispadias or hypospadias

a) Urethra opens on top of penis
b) Urethra opens on bottom of penis
c) Associated with bladder exstrophy
d) Associated with inguinal hernia
e) Associated with cryptorchidism
f) Associated with curved penis

2) Which is false?

a) Balanitis is the inflammation of the glans penis.
b) Posthitis is the inflammation of the foreskin.
c) Balanitis xerotica obliterans is a chronic, noninfectious inflammation of the glans penis.
d) Inflammation of the penis does not have to be infectious
e) Smegma occurs only in males

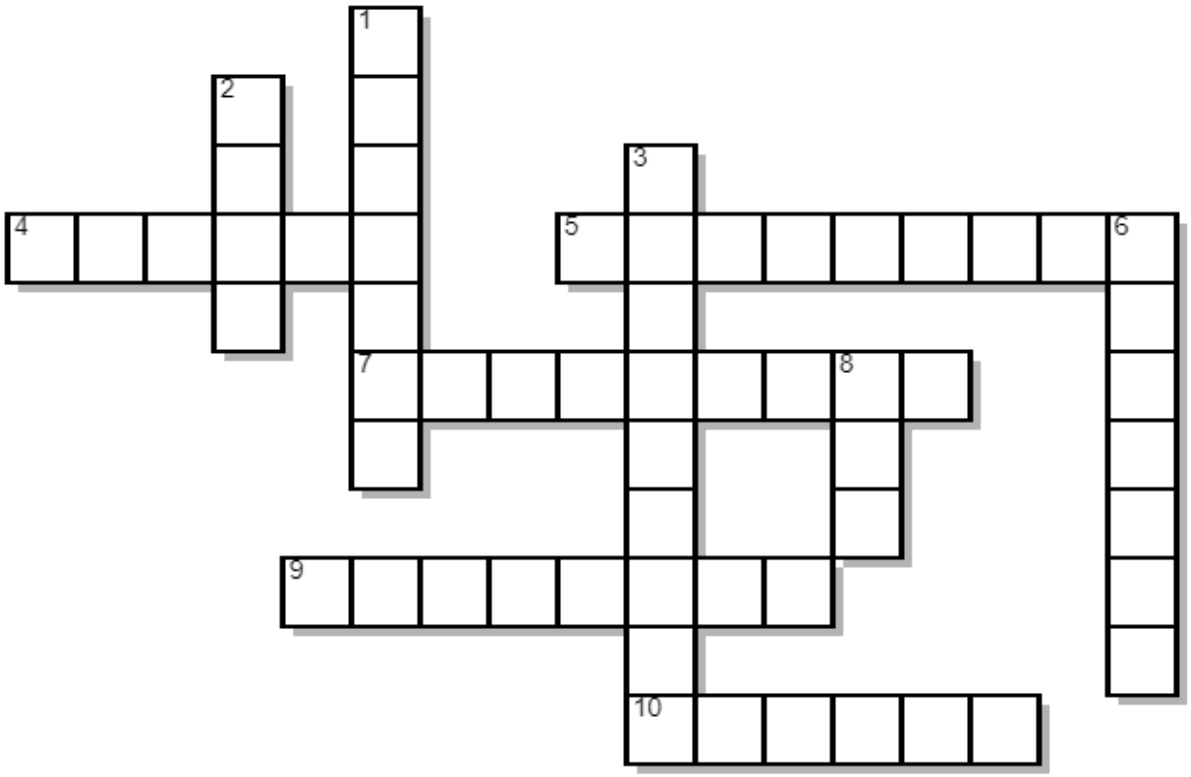
3) Which is true about Peyronie's disease?

a) It is associated with Dupuytren's contracture.
b) It is a congenital malformation
c) It will always resolve on its own or after intercourse.
d) Most of the fibrous tissue growth occurs in the corpora cavernosa
e) The tunica albuginea is not involved at all

4) Fill in the table

Feature	Bowen disease	Bowenoid papulosis	Erythroplasia of Queyrat
Location	..... or	Shaft	
Presentation		Multiple ..... papules	
Age			
Progression to carcinoma	..... – ..... %		5-10%
Association with internal cancer	33%	None	

5) Complete the puzzle (penicil recommended =))



ACROSS

4 Cysts composed of stratified columnar epithelium
5 Subtype of squamous cell carcinoma which quickly involves bones
7 Corpora ____ ruptures during penile fracture
9 Unwanted erection lasting > 4 hours
10 Build-up of dead skin cells and oils

DOWN

1 Naturally occurring bumps near genitals
2 Rate of penile cancer growth
3 Abnormal penile curvature
6 HPV type most associated with penile carcinoma
8 Type of HPV most associated with condyloma acuminatum

Section 2 – The Testis and Epididymis

2.1 – Cryptorchidism
2.2 – Inflammatory
2.3 – Testicular Torsion
2.4 – Fluid Accumulation
2.5 – Spermatic Cord and Para-Testicular Tumors
2.6 – Testicular Tumors
2.7 – Test Yourself

2.1 – Cryptorchidism

- Failure of testis to descend before birth.
- Most often unilateral and without other anomalies, but in 25% it is either bilateral or with other malformations.
    1. Coexistent malformations are more common if bilateral.
- Testis can stop at any point along the tract of descent between the abdomen and scrotal sac.
    1. Most often stop in inguinal canal, where they will then be palpable.
    2. 5-10% stop in abdomen, these are under the control of Mullerian Inhibitory Factor (MIF).
- Leads to problems with fertility.
    1. It is too warm for the sperm to develop (they like temperatures < 37C).
    2. Interstitial fibrosis
    3. Thickening and hyalinization of seminiferous tubule basement membrane.
    4. Testosterone levels are *normal* however, since Leydig cells are relatively unaffected.
- Most will descend spontaneously on their own.
- Orchiopexy if failure to descend persists until 6-12 months of age.
    1. Surgical procedure to move testicle(s) down and fixate them in the scrotal sac.
    2. This helps prevent sterility, but the ↑ risk for carcinoma (especially seminoma) persists.

MNEMONIC

Cryptorchidism
Lots of 1s
- **1**% of **1**-year-olds
- Treat by **1** year
- Generally just **1** testicle affected
- **1**0% associated with MIF
- **1**0% associated with inguinal hernias
- Most in **1**nguinal canal

CLINICAL CORRELATION

Macroorchidism and Fragile X Syndrome
- Macroorchidism = Large testicles
- X-linked dominant mutation in the FMR1 gene leading to a CGC trinucleotide repeat expansion.
- Most common cause of inherited intellectual disability.
- Also presents with large ears, ataxia, macroorchidism, and mitral valve prolapse.

2.2 – Inflammation

- Epididymis more affected than testis
    1. Exception: syphilis starts in the testis and then may progress to the epididymis if it becomes advanced enough

2.2.1 – Specific Epididymitis and Orchitis

- Orchitis: Testicular inflammation

I. Mumps

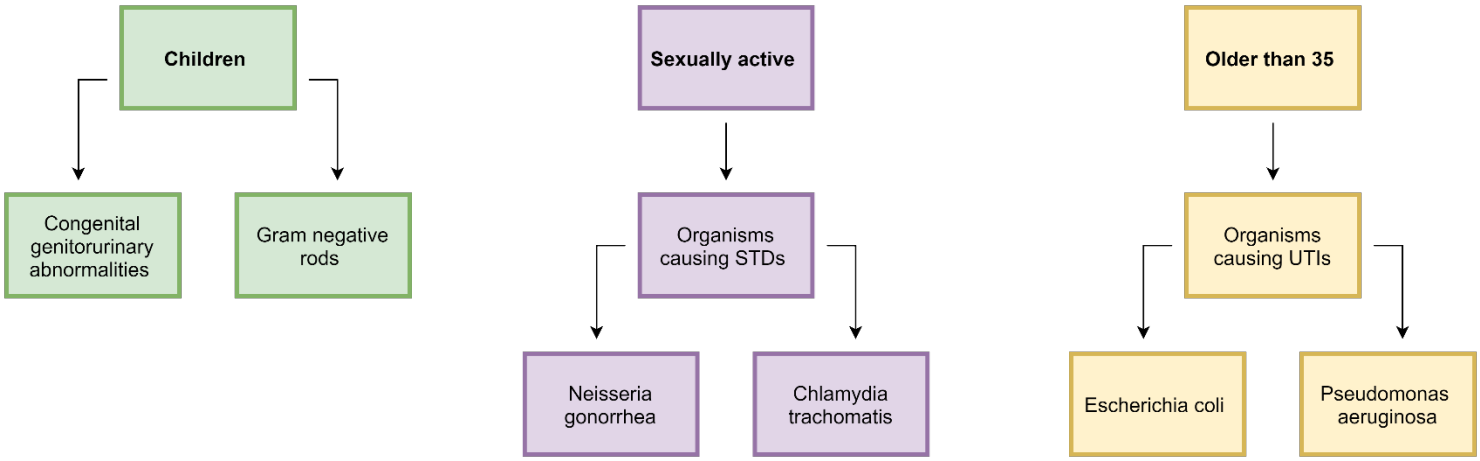
- Affects post-pubertal men who get mumps.
    1. Unlikely to have an effect in boys < 10 since they have not reached puberty yet
- Orchitis develops about a week after parotid inflammation.

II. Tuberculosis

- Beings in epididymis, may spread to testis if advanced.
- Histology shows the caseating granuloma that is classic for tuberculosis.

2.2.2 – Nonspecific Epididymitis and Orchitis

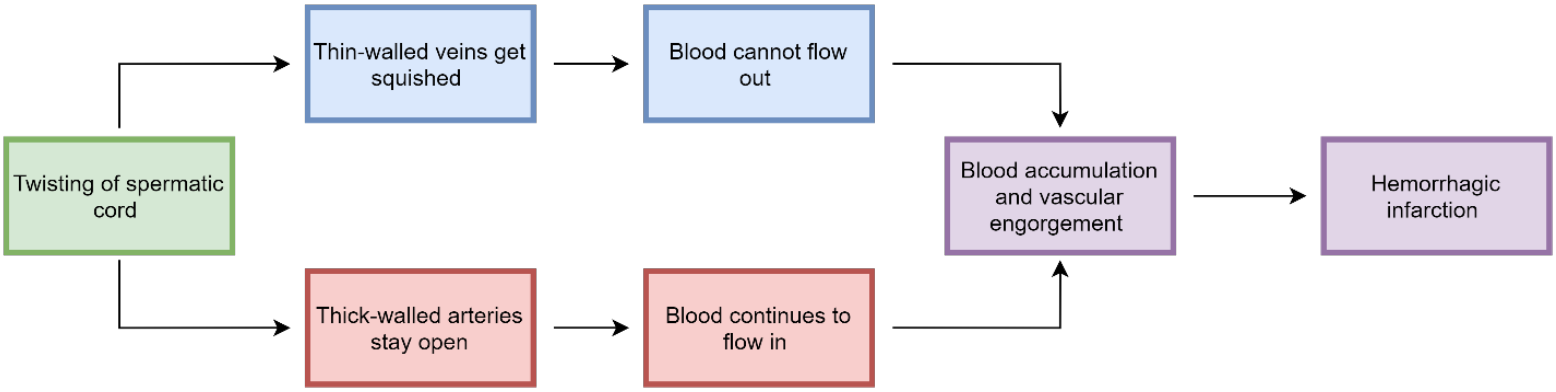
- Generally from primary UTI that ascends.
- Cause is largely aged dependent.



2.2.3 – Granulomatous (Autoimmune) Orchitis

- Affects middle-aged men.
- Presents with sudden onset of a testicular mass.
    1. May or may not be painful.
- Granulomas seen only in spermatic tubules on histology.
    1. Differentiates from tubercules which have a granulomatous reaction throughout the testis, particularly in the seminiferous tubules.

2.3 – Testicular Torsion



- Occurs without any causative injury.
- Urological emergency!
    1. Treat within 6 hours to preserve testicular function.
- Fixate testicles in the scrotal sac to prevent recurrence in the same testicle or occurrence in the other testicle.

I. Neonatal torsion

- Occurs in utero or shortly after delivery.
- No anatomic defects.

II. Adult torsion

- Presents in adolescents with sudden excruciating testicular pain.
- Associated with bell-clapper abnormality.
    1. Bilateral defect where the testicles have increased motility.

2.4 – Fluid Accumulation

I. Hydrocele

- Accumulation of serous fluid in the scrotal sac (more formally known as the tunica vaginalis) that surrounds the testicle.
- Benign and painless
- More common in kids, where it is caused by a failure of the processus vaginalis to close, allowing an open communication between the testicle and the abdominal cavity.
- In adults it is cause by a blockage of lymphatic drainage.
- Important to palpate for mass to double check there is no additional pathology.

II. Varicocele

- The spermatic vein becomes dilated due to a problem with draining.
- Presents with a swollen scrotum with dilated and visible veins on the surface. May or may not be painless.
    1. Classic "bag of worms" description refers both to visual inspection and manual palpation.
- More common on the left side
    1. The left spermatic vein drains first into the left renal vein and then the IVC.
    2. The right spermatic vein drains into the IVC right away.
- Associated with infertility
    1. Blood stasis ↑ temperature which ↓s sperm formation
- Surgical correction

CLINICAL CORRELATION

Renal cell carcinoma (RCC)

- Likes to spread into the renal vein.
- Thus, left-sided RCC is frequently connected with varicocele since the tumor will obstruct drainage of the left testicle.
- Right-sided RCC is less associated with varicocele since the tumor would need to spread much further to affect the IVC.

III. Other

- Hematocele: accumulation of blood
    1. Caused by testicular trauma, testicular torsion, or bleeding disorders.
- Chylocele: accumulation of lymphatic fluid
    1. Caused by obstruction of lymphatic drainage.
- Spermatocele: accumulation of sperm

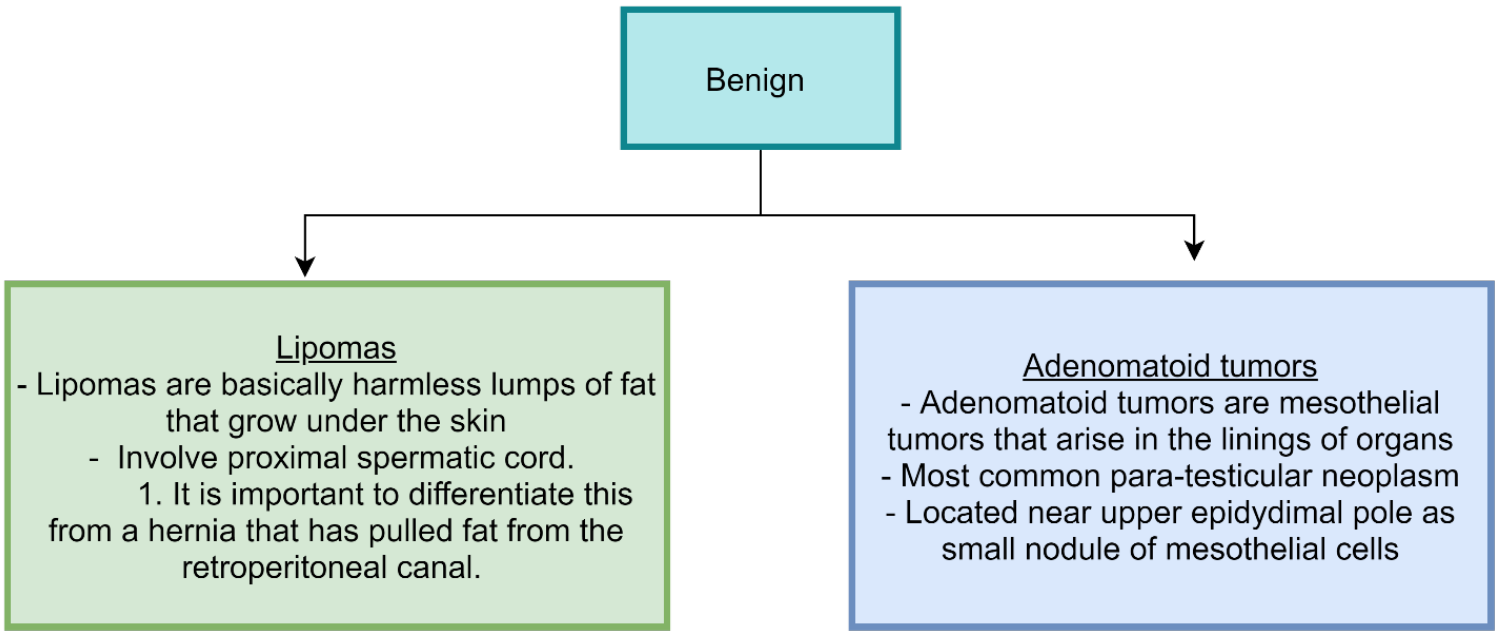
RECALL

Testicle temperature

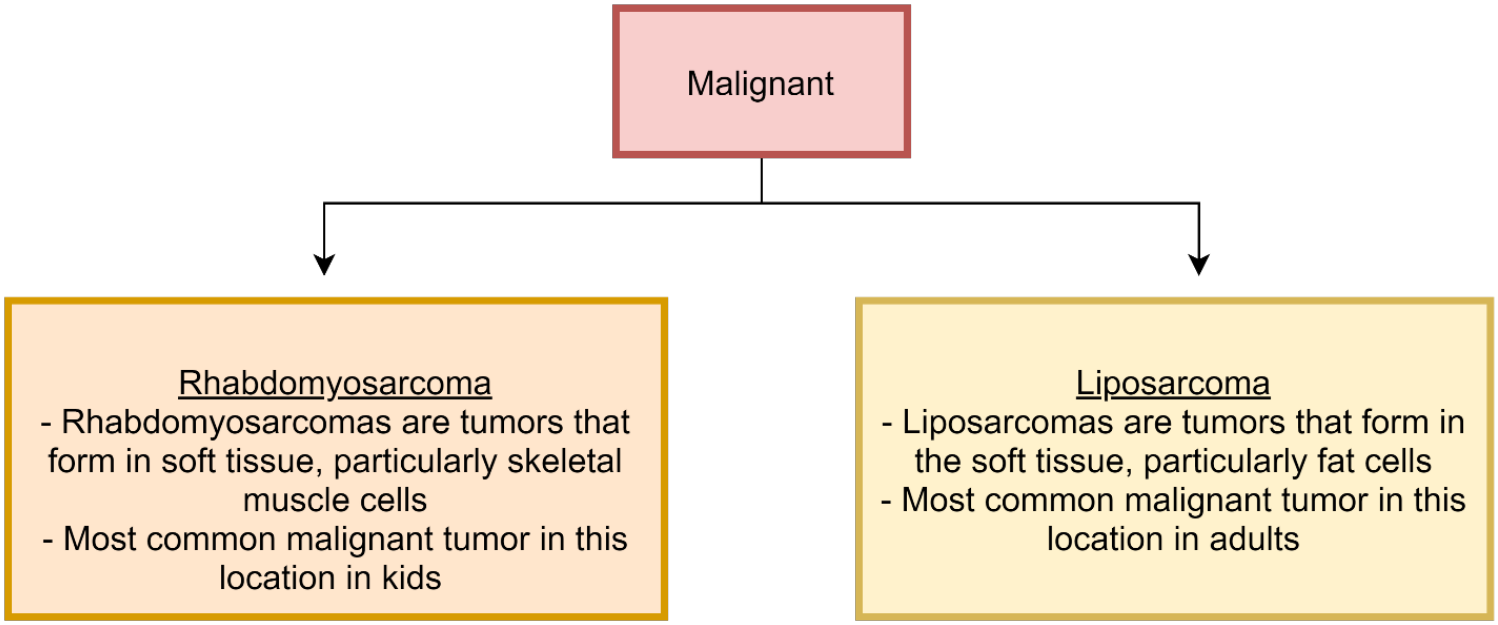
Testicles are outside of the body cavity since they need a lower temperature (by about 2 °C) to function properly.

2.5 – Spermatic Cord and Para-Testicular Tumors

2.5.1 – Benign Spermatic Cord and Para-Testicular Tumors



2.5.2 – Malignant Spermatic Cord and Para-Testicular Tumors



2.6 – Testicular Tumors

- Firm, generally painless testicular mass.
- Cannot be transilluminated.
- If found, remove by preforming an orchiectomy.
    1. Do NOT biopsy! This could cause spread of the tumor throughout the scrotum.
- Lymphatic metastasis 1st to retroperitoneal lymph nodes, then further.
- Hematogenous metastasis most common in lungs.
    1. Also common in liver, brain, and bones.

CLINICAL CORRELATION

Metastasis to testis

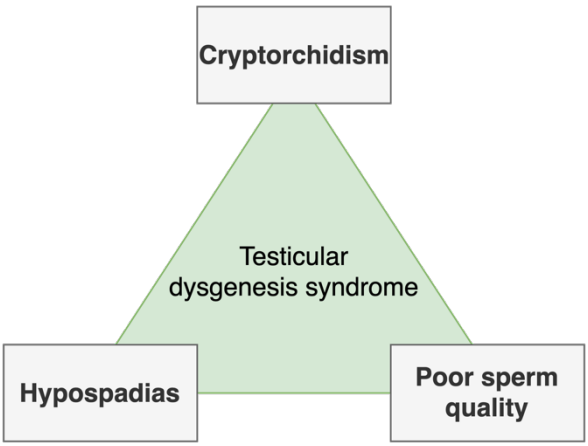
- Rather rare

- Most commonly from

1. Prostate
2. Lung
3. Skin
4. Colon
5. Kidney

2.6.1 – Germ Cell Tumors

- Generally malignant
    1. Metastasize early into retroperitoneum via para-aortic lymph nodes.
    2. However, they are often easy to treat (even in late stages). 5-year survival rate is > 95%
- Most common testicular tumors (> 90%)
- Most common malignancy in men aged 15-34.
- Risk factors
    1. Cryptorchidism is the single largest risk factor.
    2. Klinefelter syndrome is associated with germ cell tumors (especially teratomas) forming in the mediastinum. Klinefelter is also associated with in increased risk of breast cancer in males.
    3. Testicular dysgenesis syndrome (a triad of cryptorchidism, hypospadias, and poor sperm quality) increases the risk of GCTs. It can occur due to pesticide or estrogen exposure in utero.



- Arise from intratubular germ cell neoplasia (ITGCN) which first appear in utero but will not be noticeable until it becomes “activated” by puberty.
    1. Totipotent (cells can differentiate into any cell type)
- Often contain an activated mutation of c-KIT, meaning that they turn the proto-oncogene into an oncogene. Therefore, the gene will constantly be turned on and will thus continue to produce new cells.
- Prognosis is based on the differentiation between seminomas and non-seminomas, in addition to staging:

	Seminomas	Non-seminomas
Response to treatment	Good	Various
Metastasis	Late	Early
Prognosis	Good	Poor

CLINICAL CORRELATION

Lactate dehydrogenase (LDH)

- Can be used to measure tumor burden
- A heavier tumor burden will ↑ the energy demands and will thus ↑ the LDH.
- This is the case in a lot of cancers, not just GCTs.

I. Seminoma

- 50% of all GCTs
- Male equivalent of ovarian dysgerminoma.
- Good response to radiotherapy, good prognosis.

II. Spermatocytic seminoma

- Rare
- Despite its name, it is NOT actually a type of seminoma.
- Rarely metastasize
    1. Can thus be treated surgically and rarely require chemo or radiotherapy

III. Embryonal carcinoma

- More aggressive, poor response to radiotherapy, poor prognosis.
- Chemotherapy may lead it to transform into a different type of GCT.
- C-KIT negative

IV. Yolk sac tumor (endodermal sinus tumor)

- Most common testicular neoplasm in patients less than 3 years old.
    1. If it occurs in adults, it is similar to embryonal carcinoma.
- Good prognosis.
- Infiltrates visible with the naked eye.
- Schiller-Duval bodies are present in 50%
    1. Structures that look like glomeruli. The significance of this is that if you have something that histologically looks like a kidney but is located in the testis (or ovaries in women) then it is quite likely a yolk sac tumor.

V. Teratoma

- Mature fetal tissue, hence the ability to form basically any structure within the tumor.
- Pure teratomas are rare.
- 50% of other germ cell tumors present with some teratoma mixed in, hence teratoma generally occurs with another GCT.
- Presence of hemorrhage or necrosis implies likely co-existent embryonal GCT or choriocarcinoma.
- May be mature (adult-type tissue) or immature (embryonic-type and fetal-type tissue).
- If there is malignant transformation, this means that there is probably a non-germ cell tumor component within the teratoma. The teratoma should then be removed in its entirety, as it will not respond to chemotherapy once it has spread past the testicles.

VI. Choriocarcinoma

- Very malignant, poor prognosis
    1. Early hematogenous spread so distant metastasis is present early (exception to the lymphatic metastasis of other GCTs)
- It is also often small, so it may be hard to diagnose early.
    1. The metastatic lesion may actually be larger than the primary testicular tumor – the opposite of what is normally the case in cancers!
- Contains both cytotrophoblasts and syncytiotrophoblasts.
    1. Cytotrophoblasts make up the inner layer of the trophoblast. They are basically the trophoblastic stem cells.
    2. Syncytiotrophoblasts make up the outer layer of the trophoblast. They produce hCG, hence β-hCG will be elevated.

RECALL

Embryology: Trophoblasts

- These cells form the outer layer that surrounds the blastocyst.
- Provide nutrients to embryo and develop into the placenta.

CLINICAL CORRELATION

Ectopic hyperthyroidism and gynecomastia

- There are 2 types of hCG: α and β, both are produced by syncytiotrophoblasts.
- The α subunit is similar to FSH, LH, and TSH. This is why choriocarcinoma patients may present with hyperthyroidism and gynecomastia.
- The β subunit helps the placenta and fetus develop.

VII. Mixed germ cell tumors

- Most germ cell tumors are mixed.
    1. Metastasis of germ cell tumors may have different appearance than the primary tumor!
- Prognosis is based on the worst component.
    1. This makes sense since if there is one bad part that will kill you quickly then the other parts don't really matter that much, no matter how "chill" they are.
- Even is a seminoma component is present, it is classified as a non-seminoma.
- Unclassified mixed germ cell and sex cord stromal tumor
    1. Gradual testicular enlargement
    2. Does not metastasize
    3. Excellent prognosis after resection
    4. Most common in 4^{th}-7^{th} decade

CLINICAL CORRELATION

Ectopic spleen in scrotum

- Aka splenogonadal fusion syndrome.
- Often an accessory spleen
1. A small 2^{nd} spleen
2. Found in 10% of people
3. Completely benign, most people don't even know they have it.

- Usually on the left side.
- May mimic a tumor since it presents as a scrotal mass.

Germ cell tumors

	Seminoma	Spermatocytic seminoma	Embryonal carcinoma	Yolk sac tumor	Choriocarcinoma	Teratoma
Peak age	30s	> 65	20s	< 3	-	Any age
Color	Gray-white	Gray	Gray-white	Yellow-white	-	Varies, often mixed
Microscopic	- Clear cytoplasm - Large nuclei - Nucleoli - "Fried egg cell"	- Small cells appearing like secondary spermatocytes - Medium cells with round nucleus and eosinophilic cytoplasm - Giant cells	- Epithelial cells with indistinct cell borders "organized" into sheets, tubules, alveoli, and papillary structures. - Giant cells	- Schiller-Duval bodies (in 50%)[2] - Cuboidal neoplastic cells arranged into a reticular network. - Papillae	- Polygonal, regular cytotrophoblastic cells - Multinucleated syncytiotrophoblastic cells	- Mixture of different germ cell layers (mesoderm, endoderm, and ectoderm)
Positive for	- c-KIT - OCT4 - PLAP - (β-hCG)[1]	-	- OCT3/4 - PLAP - cytokeratin - CD30 - (β-hCG)[1] - (AFP)[1]	- AFP - α-1 antitrypsin	- β-hCG	Varies depending on components
Additional high yield information	- Most common -Hemorrhage and necrosis absent. -Spares tunica albuginea	- Independent of ITGCN and cryptorchidism.	-Hemorrhage and necrosis present. - Extends through tunica albuginea, thus affecting the spermatic cord and epididymis	- Associated with hyperthyroidism and gynecomastia	- Highly malignant - Small	- Benign in kids - Malignant in adults males - Occurs with other GCTs. - Large (up to 10cm)

[1]While this may be positive in that tumor, it is not the most common association.

[2] Structures that look like glomeruli. The significance of this is that if you have something that histologically looks like a kidney but is located in the testis (or ovaries in women) then it is quite likely a yolk sac tumor.

2.6.2 – Sex Cord Stromal Tumors

- Generally benign

I. Leydig cell tumor

- Occur in men 20 – 60 years old.
- Most are benign, but up to 10% may be invasive or metastatic.
- Gross pathology
    1. Circumscribed nodules with golden brown surface
- Microscopic pathology
    1. Cells with abundant granular and eosinophilic cytoplasm and undefined cell borders.
    2. Lipochrome pigment, lipid droplets, and eosinophilic
    3. Reinke crystals (rod-like cytoplasmic inclusions)
- Present with testicular mass + changes from excessive hormones.
    1. These tumors may produce androgens, estrogens, and/or corticosteroids causing additional symptoms like gynecomastia or early onset puberty

RECALL

Leydig cells
- Produce testosterone, thus regulating secondary sexual characteristics.
-Stimulated by LH

II. Sertoli cell tumor

- Present with testicular mass only!
    1. Mnemonic: sert**only** testicular mass
- Gray-white or yellow masses visible to naked eye.
- Columnar cells with trabeculae forming tubules seen microscopically.

RECALL

Sertoli cells
- Nourish sperm cells during spermatogenesis.
- Stimulated by FSH

II. Granulosa cell tumor

- Very rare in males
- Benign in kids
- Malignant in adults

2.6.3 – Testicular Lymphoma

- Most common testicular tumor in patients > 65.
- Generally bilateral
- Diffuse large B-cell non-Hodgkin lymphoma is the most common type
    1. Aggressive, most common NHL in adults
    2. Associated with Bcl-2, Bcl-6 and p53 mutations
- Disseminate widely
- Frequently involve CNS

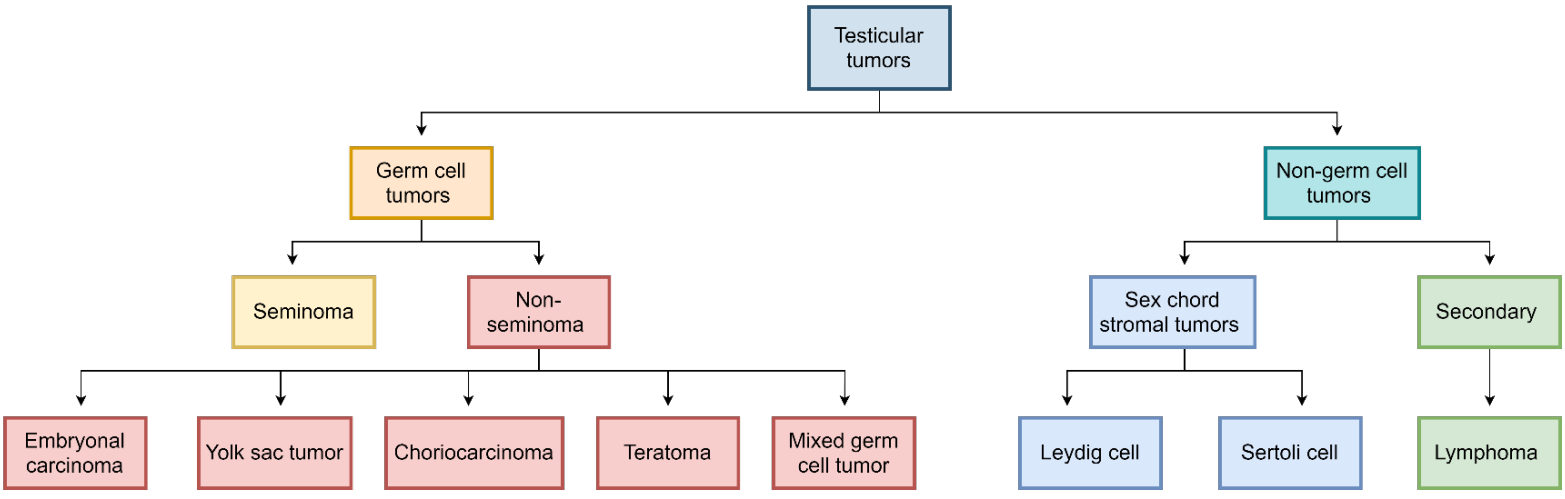
2.6.4 – Adenomatoid tumor

- Presents in 3rd – 5th decade as an asymptomatic, solitary, unilateral mass.
    1. Does not transilluminate on transillumination test
    2. Generally small, < 5 cm
    3. Grayish-white in color
- Affects para-testicular tissue
- Benign

2.6.5 – Extramammary Paget Disease

- A rare cancer which presents In 6th-7th decade as a red, scaly rash.
    1. Related to Paget disease of the breast
- Microscopic pathology: Atypical cells with large cytoplasm and vacuoles proliferating throughout the epithelium.
- Check for local carcinomas: Cancer of prostate urethra, or bladder will be present in the majority of cases.

Summary of testicular tumors



2.7 – Test Yourself

1) Which is false about undescended testis?

a) The medical word for it is cryptorchidism.
b) Most are palpable in the inguinal canal
c) It is generally bilateral
d) It should be treated surgically if it persists to their first birthday.
e) Despite normal testosterone levels, there are problems with fertility.

2) Match the age group to the most common pathogens of epididymitis and orchitis

a) Chlamydia trachomatis
b) E. coli
c) Neisseria gonorrhea
d) Gram negative rods
e) Pseudomonas

i) Children
ii) Sexually active
iii) > 35 years old

3) Which is true about testicular torsion?

a) It should be fixed within a year.
b) It occurs from intense blunt trauma to the testicles
c) It is associated with increased testicular motility
d) It is completely painless
e) It is impossible in neonates

4) Which is incorrectly matched?

a) Hydrocele – urine accumulation
b) Hematocele – blood accumulation
c) Spermatocele – semen accumulation
d) Chylocele – lymphatic fluid accumulation

5) Which is false about varicocele?

a) It is associated with renal cell carcinoma
b) it is more common on the right side
c) It is caused by a problem with venous drainage
d) It is associated with infertility
e) It feels like a bag of worms upon examination

6) Which is false about germ cell tumors?

a) They are generally benign
b) They are the most common testicular tumor
c) Cryptorchidism is the single largest risk factor
d) Seminomas are the most common individual type
e) Lactate dehydrogenase can be used to measure tumor burden.

7) Which is false about testicular tumors?

a) Biopsy is the mainstay of diagnosis

b) Most common site of hematogenous metastasis are the lungs

c) The 1st site of lymph node metastasis are the retroperitoneal lymph nodes.

d) They present as firm testicular masses

e) They are always treated surgically.

8) Which is false about testicular lymphoma?

a) It is the most common testicular tumor in the elderly

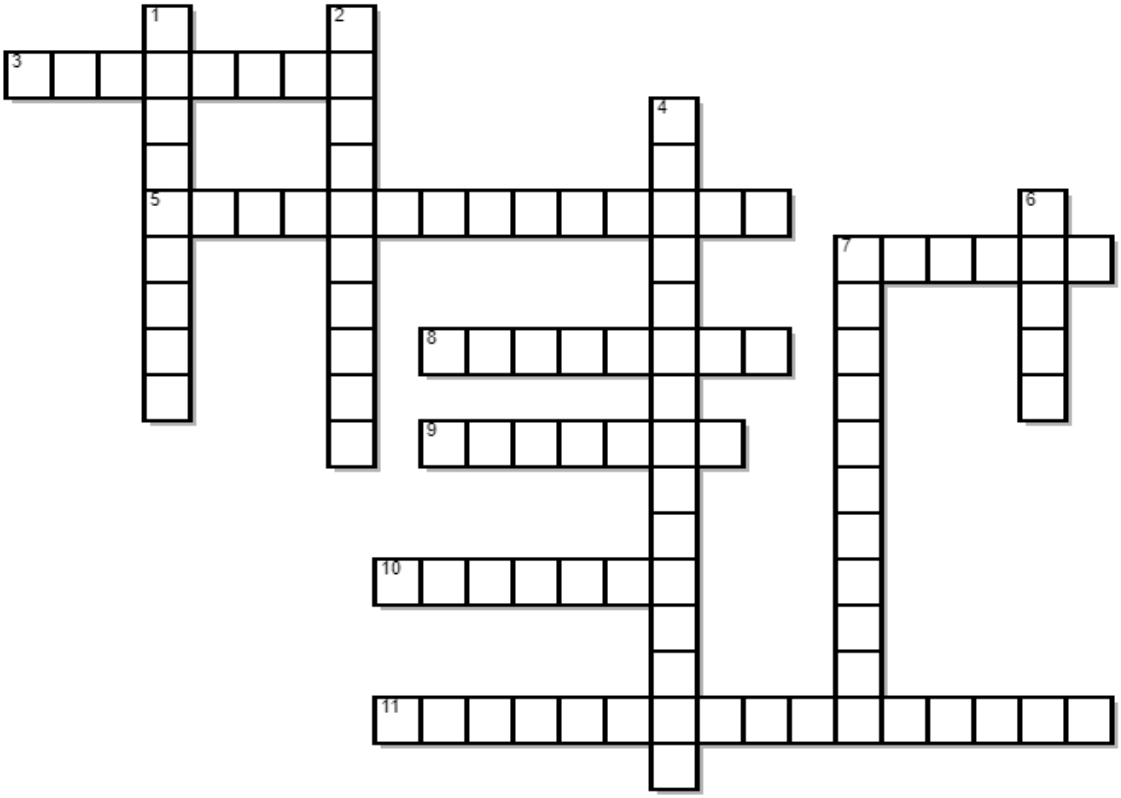
b) It is generally unilateral

c) It disseminates widely

d) It may involve the CNS

e) It may be associated with BCL-2, BCL-6, and p53 mutations

9) Crossword puzzle



ACROSS

3 Germ cell tumor which may contain teeth or hair
5 Most common malignancy in men aged 15-34
7 Tumor presenting with testicular mass excessive hormones
8 Male equivalent of ovarian dysgerminoma
9 Germ cell tumor with good prognosis
10 Tumor presenting with testicular mass only
11 Most common malignant tumor of spermatic cord in kids

DOWN

1 Germ cell tumors are _____
2 Bag of worms
4 Germ cell tumor with poor prognosis
6 Most germ cell tumors are ____
7 Most common malignant tumor of spermatic cord in adults

Section 3 – The Prostate

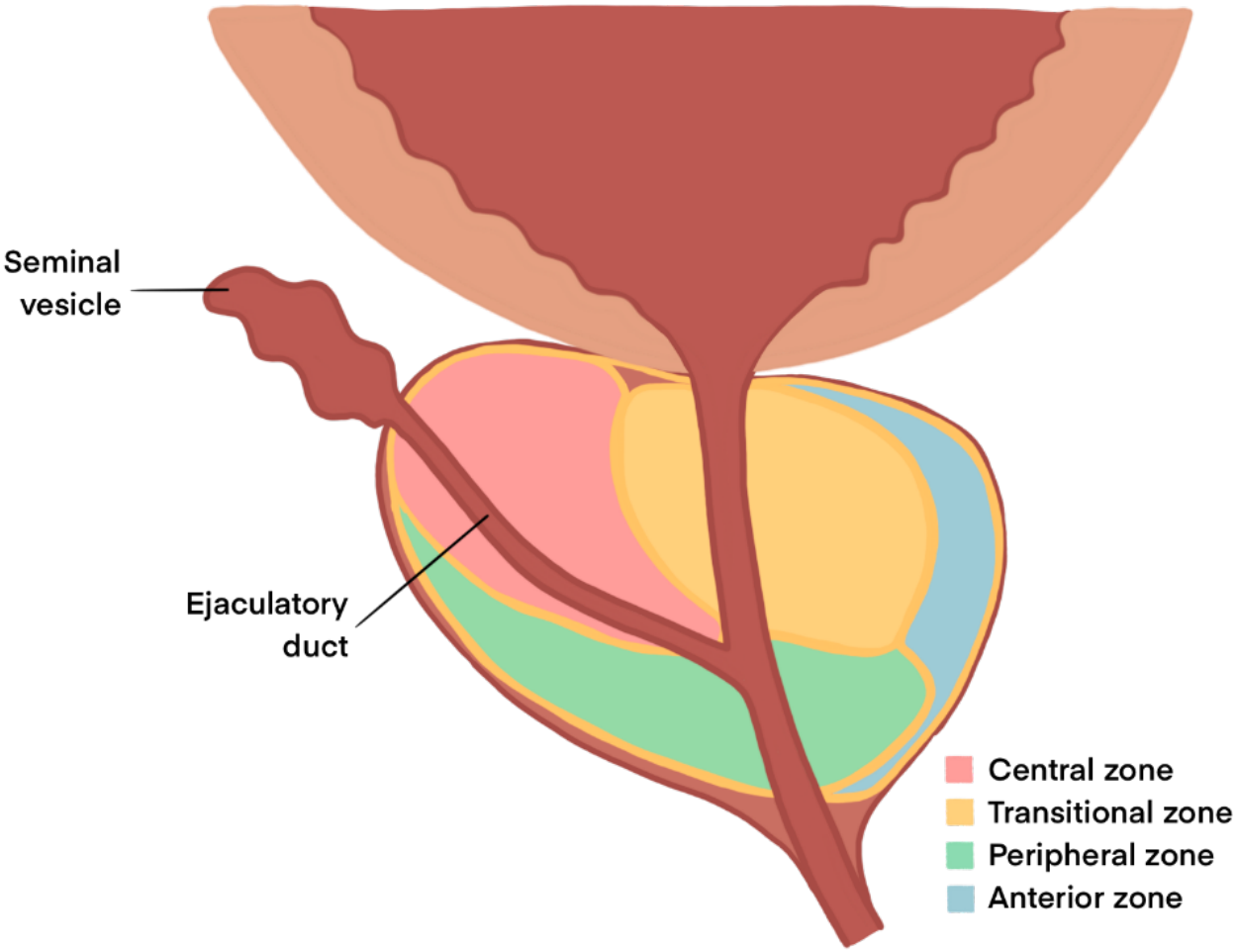
3.1 – Inflammation

3.2 – Benign Prostatic Hyperplasia (BPH)

3.3 – Prostate Cancer

3.4 – Test Yourself

Prostate anatomy



3.1 – Inflammation

- Infection of the prostate can occur due to urinary reflux, spread from other sites, or after invasive procedures.

3.1.1 – Acute vs. Chronic Prostatitis

- Patients with chronic prostatitis does not necessarily have a history of acute prostatitis

	Acute bacterial prostatitis	**Chronic bacterial prostatitis**
Definition	Acute inflammation of prostate	Chronic inflammation of prostate
Causative pathogens[1]	Young: Chlamydia trachomatis, Neisseria gonorrhea Old: E. Coli, Pseudomonas aeruginosa	
Presentation	Fever, chills, dysuria[2] May cause obstruction, retention, and abscesses Prostate is boggy and tender on DRE	Pain in lower back, suprapubic, and perineal area Pain when urinating Recurrent UTIs[3] May be asymptomatic
Blood cultures	+	-
Prostatic secretions	WBCs	WBCs + cultures

[1] If these look familiar – good job! They are the same as in orchitis.

[2] Dysuria = Panful urination

[3] Antibiotics do not penetrate the prostate very well, so bacteria find a nice little safe home here in the prostate from where they can keep reinfecting the urinary tract.

3.1.2 – Chronic Abacterial Prostatitis

- Most common form of prostatitis.
- Presents similarly to chronic bacterial prostatitis, but without the recurrent UTIs.
    1. There are no bacteria hiding in the prostate, so there will be no bacteria to keep causing the UTIs.
- WBCs seen in prostatic secretions. Cultures of prostatic secretions will be negative.
    1. The inflammation is present even when there is no causative pathogen.

3.1.3 – Granulomatous Prostatitis

- Biggest risk factor is using BCG to treat bladder cancer.
    1. Not clinically significant, do not require treatment.
- Non-specific granulomatous prostatitis may occur as well. In this case glands and acini rupture, and the secretions from this cause a local inflammation.
- Classic triad: high fever, hard prostate, prostatitis symptoms (back pain, dysuria, frequency, urgency)
    1. Actually occurs in only 20% of patients

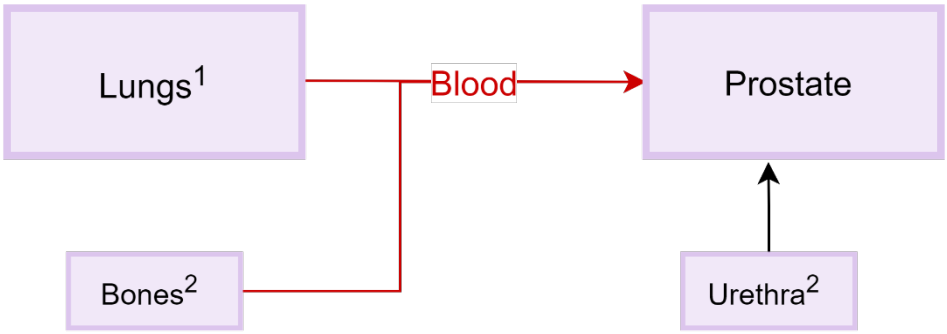
CLINICAL CORRELATION

Bacillus Calmette-Guérin

- Nonvirulent form of mycobacterium bovis.
- Used in vaccination for tuberculosis and in treatment of early-stage bladder cancer.
- When treating cancer, it promotes immunocompetent cells (such as NK cells) to enter the tumor and kill malignant cells.

3.1.4 – Tuberculosis

- Tender on palpation (DRE) when advanced.
- Generally bilateral
- Initially lesion is in the stroma, but it quickly spread to the acini.
- Caseation is frequent
    1. Tubercules typical for tuberculosis are rare however.



[1] Spread is primarily from lungs, via blood.
[2] May sometimes spread from bones or directly from the urethra, but these are much rarer.

3.1.6 – Malakoplakia

- Chronic form of inflammation, often granulomatous.
- Most associated with bladder disease but can involve any part of the genitourinary tract.
    1. Can actually involve almost any part of the body.
- Tissue reaction triggered by bacterial infection.
- Michaelis-Gutmann bodies seen under a microscope.
    1. These are aggregates of calcium and iron.
- Important to diagnose further, especially since it may look like cancer on USG.
    1. It may also coexist with cancer – some parts of the prostate may have malakoplakia while others have cancer.

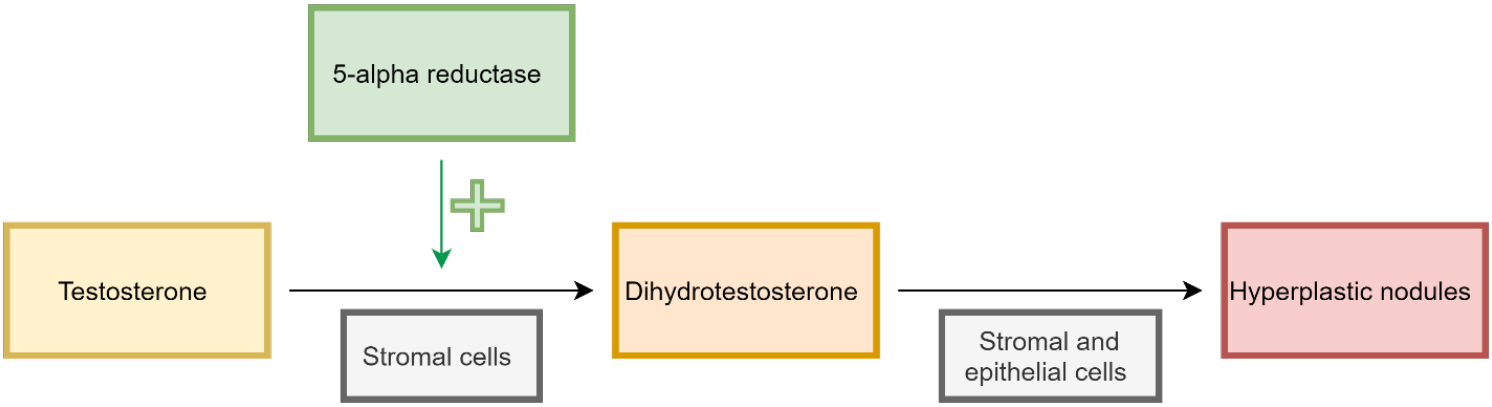
3.2 – Benign Prostatic Hyperplasia (BPH)

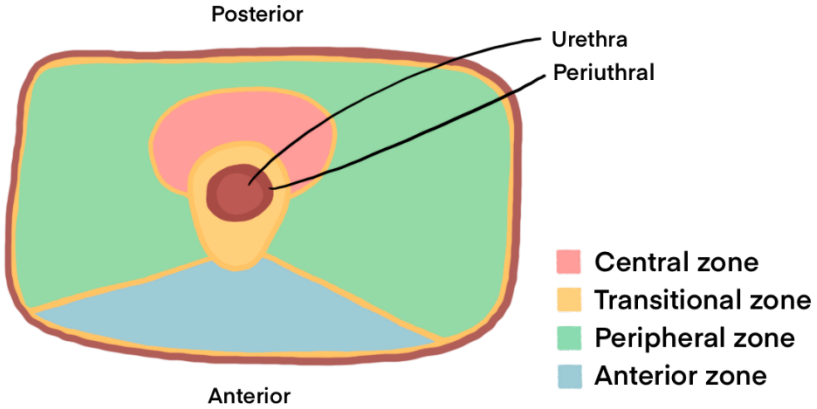
- Aka prostatic nodular hyperplasia and benign prostatic enlargement (BPE).
- The prostatic stroma and glands increase in number.
- Very common: 90% of men in their 80s
- There is NO increased risk for prostatic cancer!
- Pathogenesis involves dihydrotestosterone (DHT) (see flow chart)
    1. Androgen-dependent
- Growth occurs in the central periurethral zone of the prostate and the transitional zone.
    1. This explains why the majority of symptoms are connected with urination. (See drawing)

RECALL

Hyperplasia vs hypertrophy
- Hyperplasia: ↑ in cell number
- Hypertrophy: ↑ in cell size

Effect of testosterone, 5α-reductase, and DHT on hyperplasia

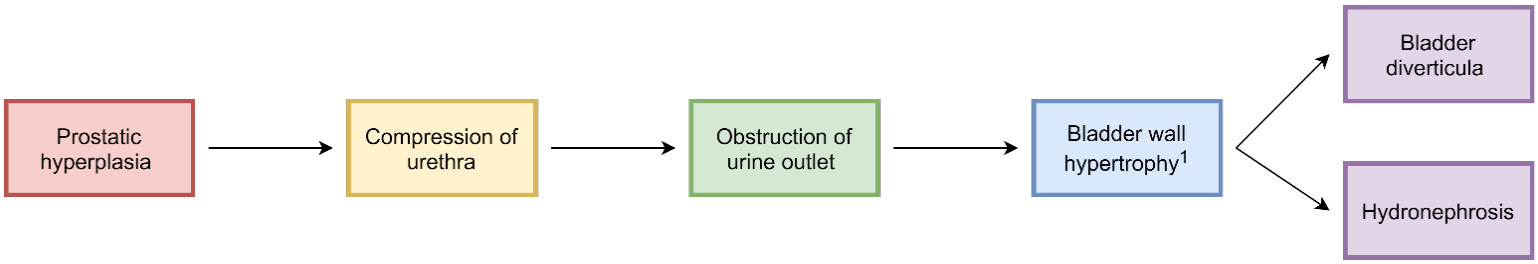




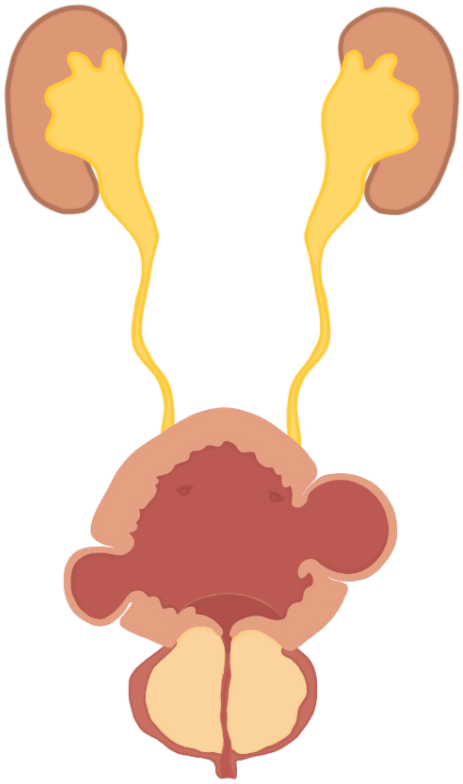
3.2.1 – Symptoms of BPH

- Problems starting and stopping urination.
- Problems with emptying bladder properly, thus leading to an increased risk of infection and hydronephrosis. The hydronephrosis may then lead to excessive dilation within the kidney, and thus cause renal failure.
- Involuntary dribbling of urine.
- Blood visible in urine microscopically.
- PSA may be slightly elevated

I. Obstructive symptoms



- *Directly* related to narrowing of the bladder neck and compression of the prostatic urethra
    1. Difficulty beginning urination
    2. Weak urine stream and straining
    3. Inability to maintain a constant urine stream
    4. Sensation of incomplete emptying and dribbling



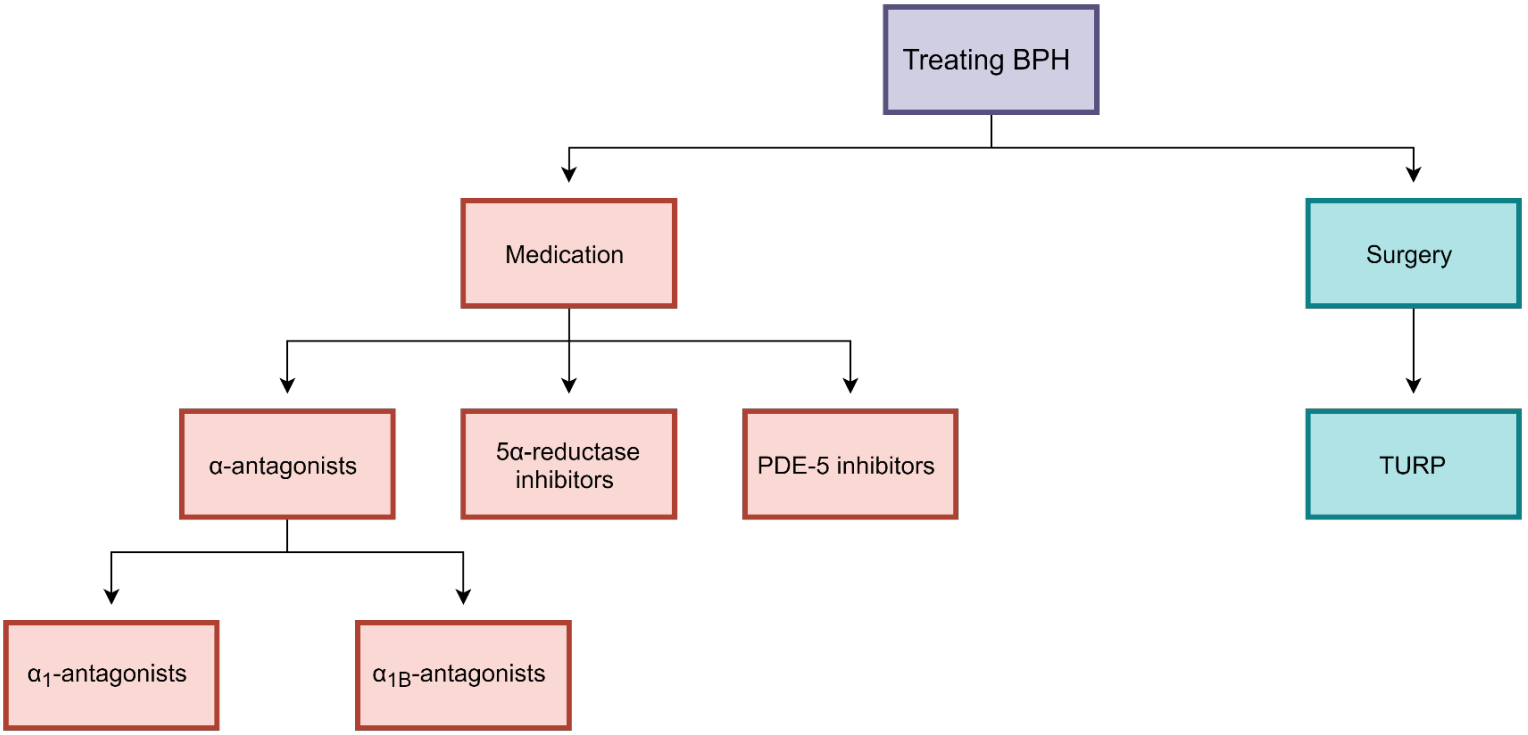
II. Irritative symptoms

- Related to storage problems cause urinary obstruction.
- Connected to the bladder's *response* to the obstruction.
    1. Urinary frequency and urgency
    2. Nocturia
    3. Cancer

PSA values in different situations

Normal	BPH	Cancer
< 4 ng/mL	4-10 ng/mL	> 10 ng/mL

I. Treatment of BPH



- α_1-antagonists (e.g.: Terazosin): Relax smooth muscle, and thus relieve obstructive symptoms.
- Selective α_{1B}-antagonists (e.g.: Tamsulosin)
    1. Does not affect blood vessels, so this is preferred to the above in patients with low or normal blood pressure.
- 5α-reductase inhibitors (e.g.: Finasteride): Inhibits DHT production
    1. Due to its inhibition of testosterone's affects it can cause gynecomastia and sexual dysfunction
- PDE-5 inhibitors (e.g.: Tadalafil): Promote smooth muscle relaxation
- Transurethral resection of the prostate (TURP)
    1. Done if pharmacological therapy did not provide sufficient symptom relief or if symptoms are very severe (for example completely unable to urinate).
    2. May cause postoperative spindle cell nodules. These are reddish nodules that can appear a few weeks/months after TURP and may mimic a tumor (particularly sarcoma) due to their high mitotic activity.

CLINICAL CORRELATION

PDE-5 Inhibitors

- Primarily used to treat erectile dysfunction.
- Smooth muscle relaxation allows blood to flow in, thus an erection can be achieved.

3.3 – Prostate Cancer

3.3.1 – Prostatic Adenocarcinoma

- Malignant
- Most common cancer in men (27% of all cancers diagnosed in men)
    1. 2nd most common cause of cancer death in men (10% of all cancer deaths in men)
    2. More common in older men – 20% of men in their 50s, 70% for men in 70s.
- Most common prostate cancer (99%)

CLINICAL CORRELATION

Prostatic ductal carcinoma

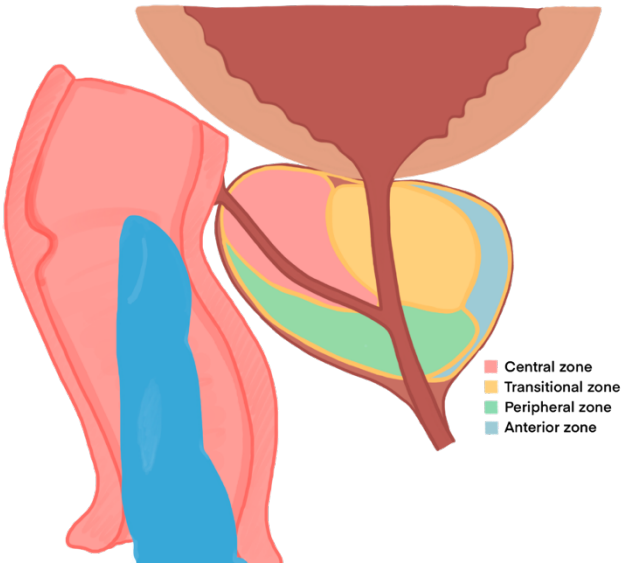
- Rare form of prostate cancer
- Involves large prostatic ducts.
- Generally grows rapidly, occupies a large space, and is more aggressive.
- Worse prognosis than cancer involving small ducts.

Cancer incidence and death rates by sex (2020)

Incidence in Men	Death in Men	Incidence in Women	Death in Women
1. Lung	1. Lung	1. Breast	1. Breast
2. Prostate	2. Liver	2. Colorectal	2. Lung
3. Colorectal	3. Colorectal	3. Lung	3. Colorectal

- Generally found in the posterior lobe (peripheral zone) of the prostate
    1. Why it can be palpated on digital rectal exam (DRE)
    2. Affects ducts and acini in peripheral regions
- Lymph node spread primarily involves pelvic lymph nodes.
    1. Poorly differentiate carcinomas may instead metastasize to left supraclavicular and mediastinal lymph nodes.
- Bone is the most common location of metastasis.
    1. Presents with bone pain, especially in the lumbar and pelvic area.
    2. Lesions are primarily osteoblastic (bone is being built), thus forming sclerotic lesions. This means that alkaline phosphatase, a marker of osteoblast activity, will be ↑. On x-ray, these lesions will mimic those of Paget's disease and osteosarcoma.
    3. Though rare, osteolytic lesions may also be found and are associated with pathological fractures.
    4. PSA and prostatic acid phosphatase (PAP) will also be ↑ed.
- Prostate cancer also like to spread to the liver, lungs, and adrenals.

I. Screening



- Starts at age 50
- Digital rectal exam allows for palpation of the prostate, particularly the posterior zone
- Prostate specific antigen (PSA)
    1. Was once used frequently to diagnose cancer. If you are going to use it, you need an ↑ed value on 2 sperate occasions.
    2. However, it is not very effective since most elderly men will have an elevated PSA. It now plays a larger role in monitoring for response to treatment (want it to ↓) and checking for recurrence (it will ↑).
    3. A PSA > 4 indicates may indicate preforming a biopsy.
- Prostate acid phosphatase (PAP) may be ↑
- Back pain: Though this has a massive differential diagnosis, if you have an adult/older man presenting with back pain it's a good idea to check for prostate cancer, especially if they also have weight loss, fatigue, and urinary symptoms.
- If urinary symptoms are present from cancer, this means that the cancer is quite advanced since it needed to spread a lot to be able to affect the urethra.

Guidelines to interpreting DREs

Normal	Prostatitis	BPH	Cancer
Painless	Painful	Painless	Painless
No masses	Swollen	Homogenous symmetric mass	Asymmetric
Rubbery	Boggy[1]	Rubbery	Nodules

[1] This is the term often used to describe an infected prostate. Basically it means squishy.

II. Staging

- Staging refers the assessment of tumor size and spread.
- TNM scale assesses:
    1. Size and local invasion
    2. Spread to lymph nodes
    3. Distant metastasis

III. Grading

- Grading determines how much differentiation cells have undergone.
- Gleason score is based on histological assessment of numerous different samples from various areas of the prostate (done under transrectal USG guidance). Two samples of the most prevalent histologies are chosen, each is graded on a pattern scale of 1-5.
    1. Most important scale for grading prostate cancer.
    2. Mnemonic: **G**rade with **G**leason

CLINICAL CORRELATION

Gleason score

The scores from two areas are addedd and a total score of 2-10 is determined.

1. Score ≤ 6: good prognosis

2. Score 7: moderate prognosis

3. Score ≥ 8: poor prognosis

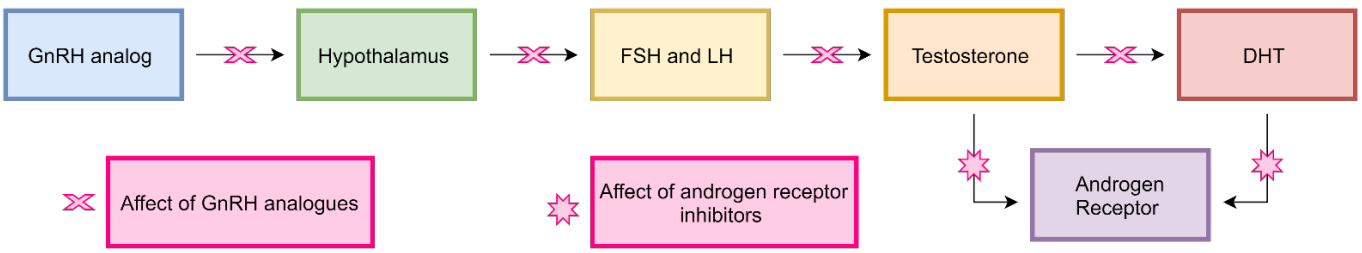
Gleason Pattern	Histological findings	Meaning
1	Small uniform glands	Well differentiated
2	↑ amount of stroma between glands	
3	Margins infiltrate distinctly	Moderately differentiated
4	Neoplastic glands forming irregular masses	Poorly differentiated/anaplastic
5	Glands are only formed occasionally	

IV. Prognosis

- Depends on stage, grade, PSA, surgical margins, and perineurial and angiolymphatic invasion.
    1. Surgical margins: if there are abnormal cells on the edge of the resection, then it is likely there are still some tumor cells left in the body, and thus a worse prognosis.
    2. Perineurial invasion: local invasion of the tumor to the area surrounding the nerve.
    3. Angiolymphatic invasion: local invasion of the lymph and blood vessels.

V. Treatment

- Localized disease: cut it out with a prostatectomy.
- Advanced disease: hormonal suppression with continuous GnRH analogues to reduce testosterone and DHT and androgen receptor inhibitors prevent testosterone and DHT from exerting an effect.



3.3.2 – Prostatic Intraepithelial Neoplasia (PIN)

- Precancerous condition in which the prostate cells begin to look and behave abnormally.
- Primarily affects two areas:
    1. Linings of the acini (the ducts the produce seminal fluid and give the prostate its spongy appearance).
    2. The linings of the ducts that later connect to the ejaculatory duct.
- The epithelial cells forming the lining become abnormal, however the lining itself remains intact.
    1. This differentiates from prostate cancer in which the lining is damaged and the cancer infiltrates into the gland.
- Does not cause an elevation in PSA .

	Low grade PIN	**High grade PIN**
Cells	Near normal	Abnormal (ex: large nucleus)
Likelihood of progression to cancer	Unlikely	Likely
Age	Young men	All
Location	General	Posterior/peripheral (same area as cancer!)
Chromosome number	Diploid[1]	Aneuploid[2]
What's next?	Not much, can repeat biopsy	Repeat biopsy[3]

[1] Have a pair of each type of chromosome

[2] Have an abnormal number of chromosomes

[3] If biopsies continue to be non-cancerous, the risk of progression to carcinoma drops continuously.

3.4 – Test Yourself

1) Match the descriptions to the type of prostatitis

a) Positive blood cultures
b) Has a classic triad
c) Negative blood cultures
d) Most common form of prostatitis
e) Boggy and tender prostate on DRE
f) BCG used to treat bladder cancer is the biggest risk factor
g) Recurrent UTIs

i) Acute bacterial
ii) Chronic bacterial
iii) Chronic abacterial
iv) Granulomatous

2) Which is false about tuberculosis when it comes to the prostate?

a) The prostate is tender on palpation
b) Initial lesion is in the stroma
c) Caseation is extremely rare
d) It may spread from the bone, lungs, or urethra
e) Its generally bilateral

3) Which is false about BPH?

a) Autopsies of most elderly men will reveal BPH
b) There is a strong association with an increased risk of cancer
c) It is sometimes referred to as BPE
d) It occurs in the central zones of the prostate
e) It can present with either obstructive or irritative symptoms

4) What is true about PSA?

a) Any increase is pathological
b) It stands for Prostate Sensitive Antigen
c) It is useless in monitoring patients after treatment
d) Normal values are < 4ng/mL
e) A one-time elevation alone can be used to diagnose cancer

5) Which of these is NOT a treatment for BPH?

a) α1-antagonists
b) selective α-1B antagonists
c) PDE-5 stimulators
d) surgery
e) 5α-reductase inhibitors

6) Which is false about prostate cancer metastasis?

a) The most common site of metastasis is the bones
b) The most common lymph nodes involved are pelvic lymph nodes
c) Liver, lungs, and adrenal metastasis is common
d) Back pain may indicate metastasis
e) It never causes osteoblastic lesions

7) Which is false about prostate cancer?
a) It is the most common cancer in men
b) It is the most common cause of cancer death in men
c) It primarily grows in the posterior lobe
d) Urinary symptoms indicate advanced cancer
e) DRE is a method of screening

8) Match!

a) PSA	i) screening
b) DRE	ii) grading
c) Gleason	iii) staging
d) TNM	

9) Which is false about prostate cancer?
a) The lowest possible score in Gleason scale is 1
b) Prostate cancer is treated with prostatectomy
c) Hormonal suppression can be used in advanced disease
d) The prostate is painless
e) Nodules can be palpated on DRE

10) Which is false about PIN?
a) Low grade PIN is NOT associated with an increased risk of cancer
b) PSA is NOT elevated
c) It primarily affects linings of acini and pancreatic ducts
d) High grade PIN is guaranteed to transform into cancer
e) PIN stands for prostatic intraepithelial neoplasia

Section 4 – Male Infertility

4.1 – Overview
4.2 – Pre-Testicular Causes
4.3 – Testicular Causes
4.4 – Post-Testicular Causes
4.5 – Test Yourself

4.1 – Overview

- Infertility is defined as the inability of two people of the opposite sex together for 12 months despite regular unprotected vaginal intercourse (2+ times a week)
    1. 1/3 of causes from male only
    2. 1/3 of cause from female only
    3. 1/3 of cause from both partners.
    4. Affects up to 15% of sexually active couples.
- The causes of male infertility are generally divided into pre-testicular, testicular, and post-testicular. There are some causes that may have their effect in numerous places (especially genetic syndromes). We will be discussing these topics where they have their largest affect.
    1. Cause cannot be identified in up to 50% of cases

CLINICAL CORRELATION

Approaching infertility in the clinic

- When a couple presents to the clinic with problems conceiving, it is important to ask about partner choice and methods of intercourse.
- This is now especially true in Poland since sexual education was banned (2020).

4.1 – Pre-Testicular Causes

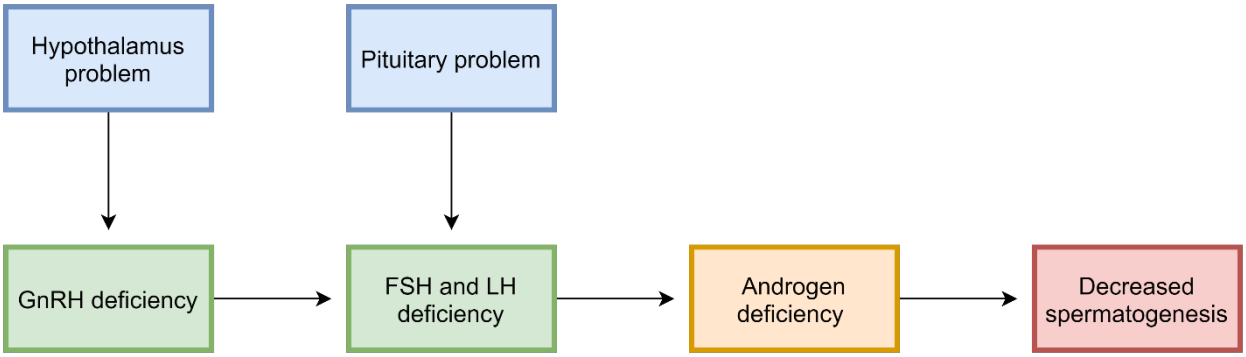
- As the name implies, these are causes whose origins lie before the testicles.
- The vast majority of these are connected to endocrinological abnormalities.
    1. Hypothalamic causes alter GnRH.
    2. Pituitary causes alter LH and FSH.
- The causes discussed here will alter the testicular function through some mechanism.

Hypothalamic-pituitary axis	- Hypothalamic abnormalities cause problems with GnRH - Pituitary abnormalities cause problems with FSH and LH - Both cause androgen deficiency
	- Panhypopituitarism and gonadotropin deficiency will lead to ↓ FSH and LH
	- Pituitary tumors cause ↑ PRL[3], which stimulates dopamine, which will ↓ FSH and LH
Thyroid	- Both hypo- and hyperthyroidism cause ejaculatory problems
Adrenal	- Adrenal insufficiency and 17-α hydroxylase deficiency[1] → ↓ androgen production → ↓ libido and ↓ spermatogenesis
Drug-related	- Steroids inhibit FSH and LH production[1]
Psychosexual	- Inability to be aroused prevents proper penetration

[1] 17α-hydroxylase deficiency is a type of congenital adrenal hyperplasia.

[2] FSH and LH help make testosterone but when you supply it from an outside source, the body is tricked into thinking that it doesn't need to make anymore. Reversible when you stop the steroid administration.

Hypothalamic–pituitary axis



Prolactin-dopamine axis

Syndromes associated with pre-testicular infertility

Isolated LH deficiency	Testosterone cannot be produced
Biologically inactive LH	LH is being produced but it doesn't do anything, so no testosterone
Kallmann syndrome	Both FSH and LH are deficient Also presents with anosmia[1]
Prader-Willi syndrome	Deletion/mutation of paternal chromosome 15 + maternal silencing Associated with cryptorchidism, hypogonadism[2], and small genitals Will also present with a ↓ IQ, massive appetite, and short stature
Laurence-Moon syndrome	Hypogonadism[2] Spastic paraplegia[3], ↓ height, ↓ IQ
Bardet-Biedl syndrome	Hypogonadism[2] Retinitis pigmentosa[4], polydactyl[5], obesity, ↓ height, ↓ IQ

[1] Lack of the sense of smell

[2] ↓ function of gonads

[3] Weakness and spasticity of all 4 limbs

[4] Damage of retina/photoreceptors → vision loss (night blindness, tunnel vision)

[5] > 5 fingers on a hand or toes on a foot

4.2 – Testicular Causes

Varicocele	Problem with vascular drainage causes an ↑ in temperature and thus ↓ sperm formation
Trauma	Testicular rupture and torsion can damage sperm-producing cells
Infection	Infection causes problems with sperm formation and ejaculation. Includes orchitis, epididymitis, seminal vesiculitis, and urethritis.
Intoxication	Toxins can damage cells that produce testosterone and sperm. These include medications (ex: for cancer) alcohol, tobacco, and certain pesticides.
Chromosomal abnormalities	Klinefelter syndrome damages Leydig cells and thus prevents testosterone formation
	Y chromosome microdeletions of the AZF gene will lead to ↓ sperm production
Developmental abnormalities	Undescended testis will remain at a higher temperature and thus have problems with sperm production
	Absence of ejaculatory ducts or sperm producing cells[1] prevents sperm from being ejaculated. Sperm may be malformed[2]
Abnormalities of androgen synthesis[6]	Lack of 5α-reductase will ↓ testosterone and thus ↓ libido and spermatogenesis[7]

[1] In vanishing testis syndrome, there are no testis. In Leydig cell aplasia, cells do not respond to LH.

[2] In immotile cilia syndrome, the sperm lack cilia and thus cannot move to the egg.

[6] External genitalia will be female or ambiguous. Karyotype will by XY (male).

FUN FACT

Bond, James Bond

- Semen can be used as invisible ink - It was used by the British Secret Intelligence Service during WWI.
- Now you know, do what you will with this information.
- No, I'm not joking.

4.3 – Post-Testicular Causes

- As the name implies, these are causes whose origins lie after the testicles.
- The vast majority of these are connected to impaired release of sperm.

Ductal obstruction	Inability to get the sperm out prevents traditional impregnation (Sperm is still viable within testicle) Can be caused by damage during surgery, genital tract infections, or cystic fibrosis
Ejaculatory problems	Inability to get the sperm out prevents traditional impregnation. These include retrograde ejaculation[1], premature ejaculation, and anejaculation[2].
Auto-immune	A damaged blood-testis barrier can lead to formation of anti-sperm antibodies
Developmental abnormalities	Penile malformations complicate penetration. These include hypospadias, epispadias, Peyronie's, and chordee.
Androgen insensitivity	Androgen receptor is unresponsive to stimulation

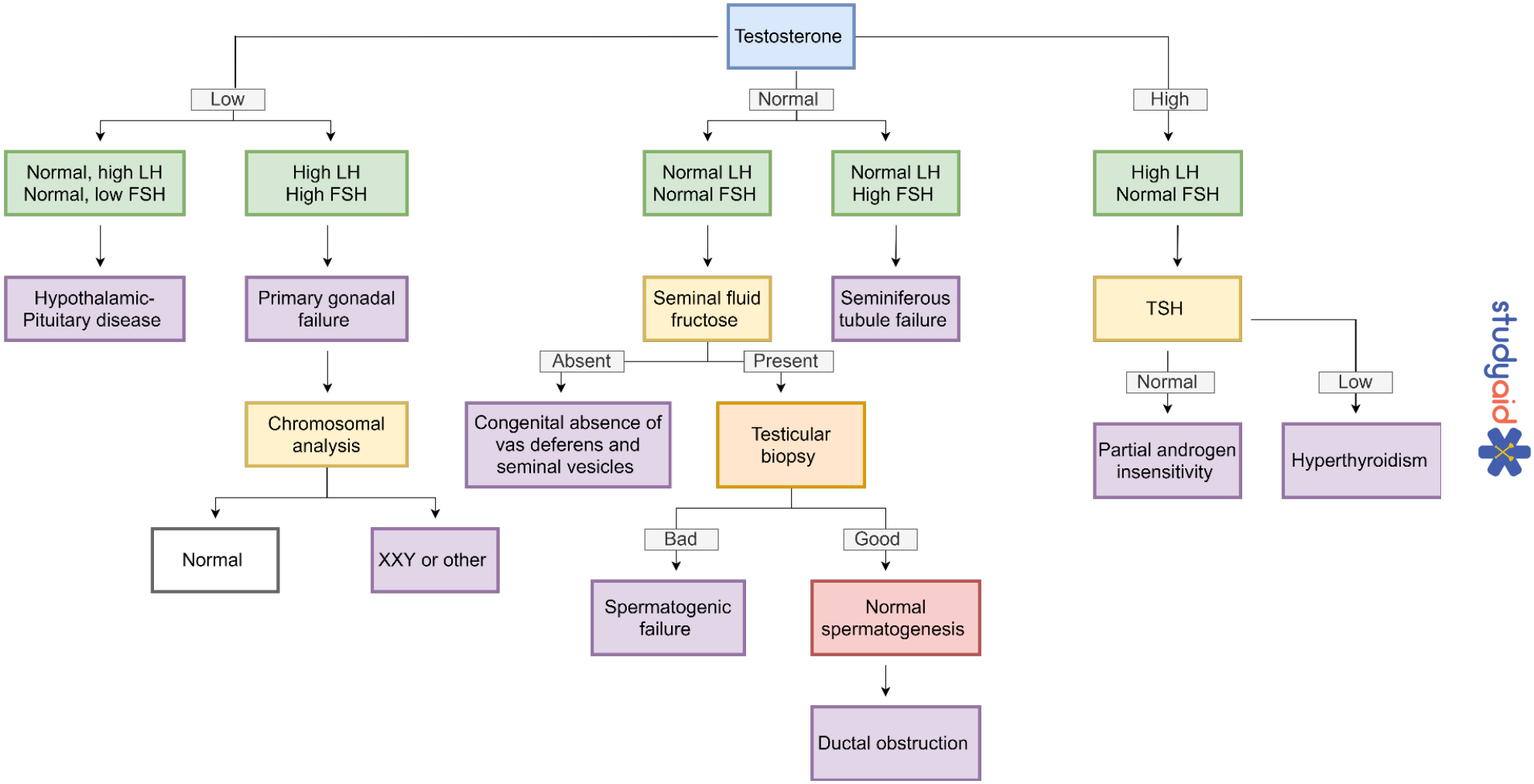
[3] Retrograde ejaculation: Sperm is ejaculated into the bladder instead of out of the penis

[4] Anejaculation = Lack of ejaculation. Associated with diabetic nerve damage.

CLINICAL CORRELATION

Adherence to treatment in diabetes

- Getting patients to stick to treatments, especially those that limit their lifestyle if often difficult.
- Most male patients, especially young ones, become most motivated to treat their diabetes properly when informed of likely decrease in sexual function and pleasure if they continue to disregard their treatment.


Testosterone
Low
Normal
High
Normal, high LH
Normal, low FSH
High LH
High FSH
Normal LH
Normal FSH
Normal LH
High FSH
High LH
Normal FSH
Hypothalamic-
Pituitary disease
Primary gonadal
failure
Seminal fluid
fructose
Seminiferous
tubule failure
TSH
Absent
Present
Normal
Low
Chromosomal
analysis
Congenital absence of
vas deferens and
seminal vesicles
Testicular
biopsy
Partial androgen
insensitivity
Hyperthyroidism
Normal
XXY or other
Bad
Good
Spermatogenic
failure
Normal
spermatogenesis
Ductal obstruction

4.4 – Test Yourself

1) What is false about infertility?
a) Causes are divided equally between male, female, and a combination of both
b) It is defined as inability to conceive despite regular, vaginal sex for over a year.
c) Cause is almost always identified
d) It can be caused by genetic abnormalities
e) It can be caused by testicular trauma

2) Which of the following is LEAST commonly involved in infertility?
a) GnRH
b) LH
c) FSH
d) GH
e) Testosterone

3) Which of these is NOT a cause of infertility?
a) Steroid abuse
b) Hyperprolactinemia
c) Hypothyroidism
d) Hyperthyroidism
e) all above are

4) AZF microdeletions will cause what?
a) Nothing
b) Problems forming sperm
c) Testicular hypertrophy
d) Obstruction of ejaculatory ducts
e) Glow in the dark sperm

5) What is the most likely diagnosis if testosterone, LH, FSH, and seminal fluid are normal?
a) Ductal obstruction
b) Kleinfelter
c) Hypogonadotropic hypogonadism
d) Androgen insensitivity
e) Hyperthyroidism

PART 3 – SEXUALLY TRANSMITTED INFECTIONS

Section 1 - Bacteria

1.1 – Chlamydia Trachomatis
1.2 – Neisseria Gonorrhea
1.3 – Gardnerella Vaginalis
1.4 – Treponema Pallidum
1.5 – Klebsiella
1.6 – Hemophilus Ducreyi
1.7 – Test Yourself

CLINICAL CORRELATION

Treating partner
It is always important to inform and treat all sexual partners.

1.1 – Chlamydia Trachomatis

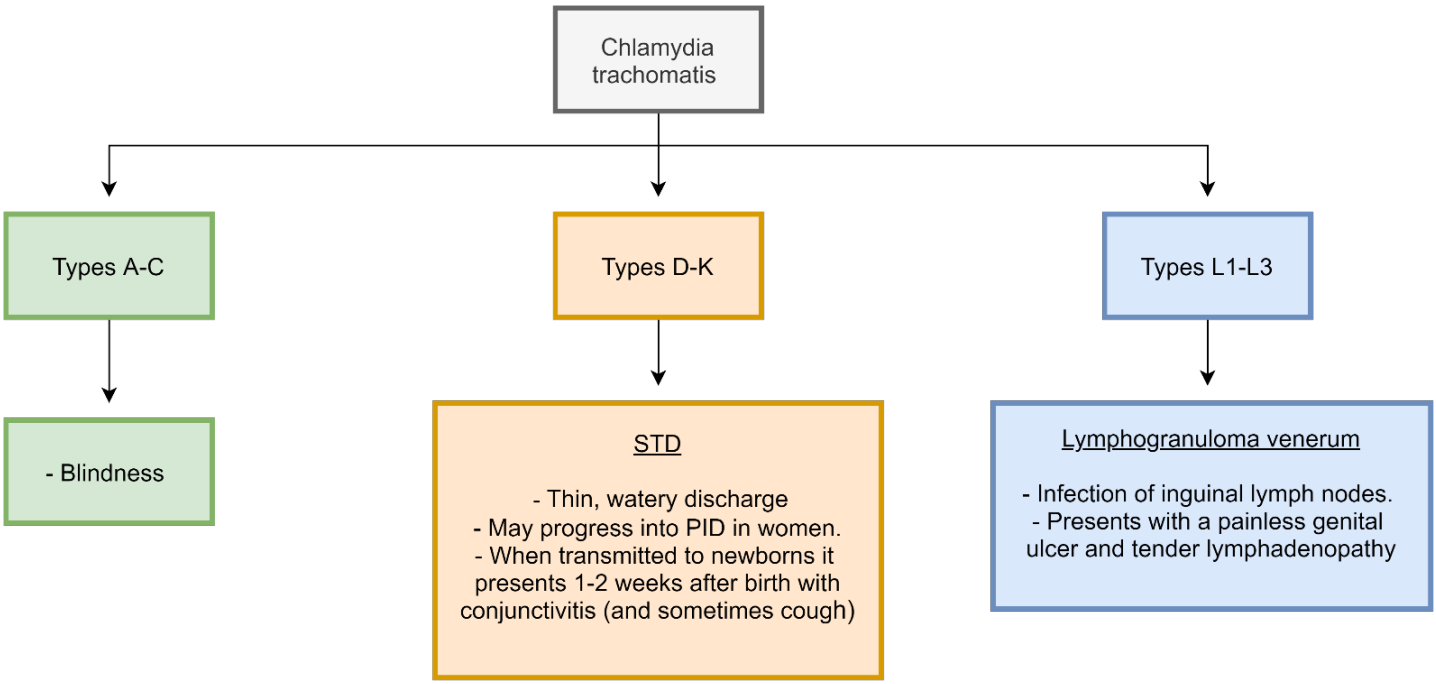
- Stains poorly (gram intermediate)

MICROBIOLOGY RECALL

Other Chlamydias
- Chlamydia pneumoniae: causes walking pneumonia in the elderly.
- Chlamydia psittaci: causes pneumonia in bird keepers.

I. Presentation

- Reiter syndrome: uveitis + urethritis + arthritis
    1. Arthritis most commonly in knee or sacroiliac joint
    1. Mnemonic: **can't see, can't pee, can't climb a tree**



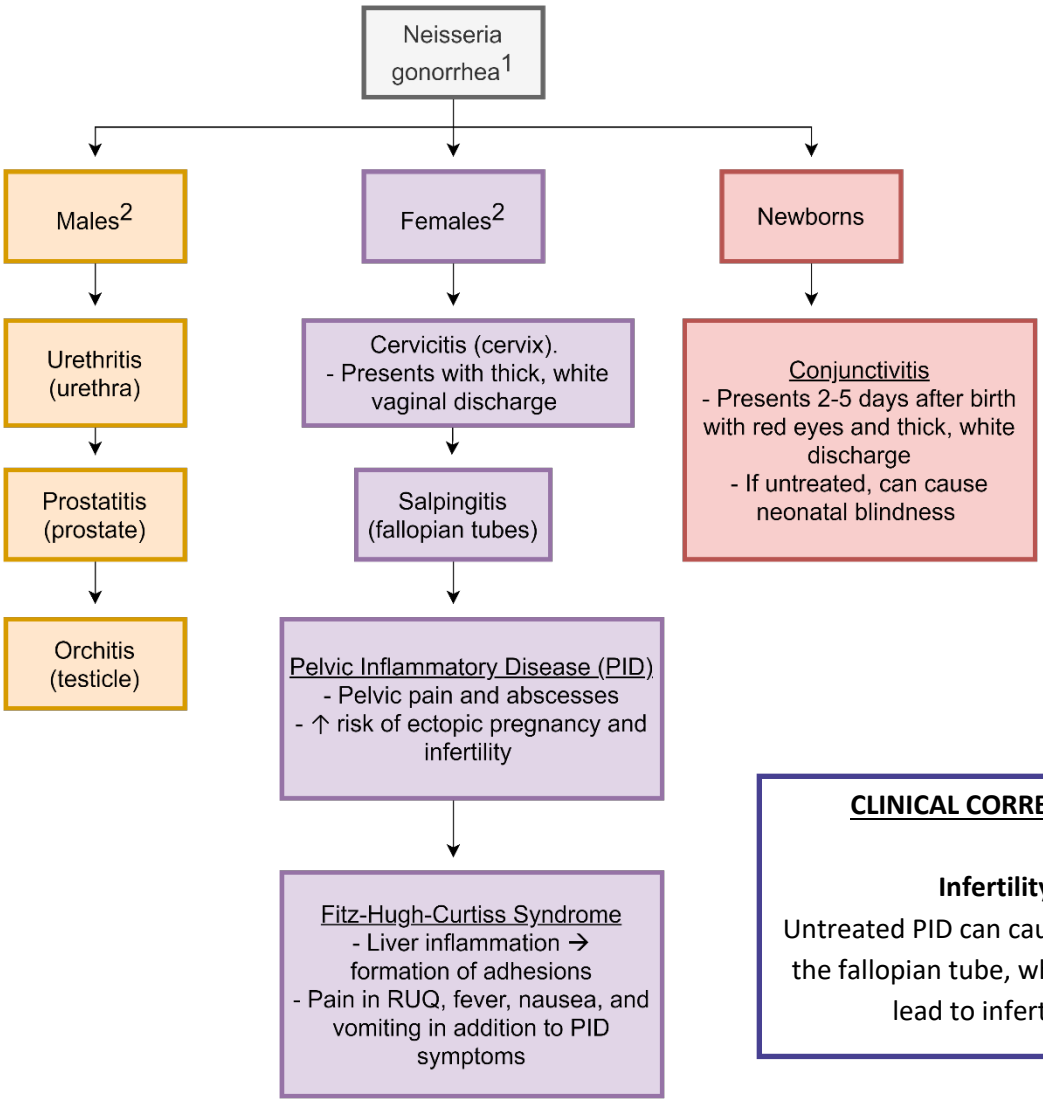
II. Treatment

- Treat with macrolides (ex: azithromycin).
    1. Due to frequent coinfection, also treat for gonorrhea with ceftriaxone.

1.2 – Neisseria Gonorrhea

- Gram negative diplococcus

I. Presentation



CLINICAL CORRELATION

Infertility

Untreated PID can cause scarring of the fallopian tube, which can then lead to infertility.

[1] Neisseria can also cause arthritis (particularly of the knee). If you have a young, sexually active patient with arthritis, consider gonorrhea as a possible cause.
[2] Ascending pelvic inflammation

II. Treatment

- Treated with ceftriaxone
    1. Due to frequent coinfection, also treat for chlamydia with macrolides.
- If antibiotics are insufficient for Fitz-Hugh-Curtis, you can cut the adhesions laparoscopically.
- Prevent STD with condoms. Prevent conjunctivitis with erythromycin eye ointment at delivery.

1.3 – Gardnerella Vaginalis

- Gram intermediate/variable rod

I. Presentation

- Amsel criteria, need 3 out of 4 to diagnose (occasionally 2 is enough)
    1. Thin, grayish-white vaginal discharge. Smells bad, often like fish.
    2. Increased vaginal pH (normal vaginal pH is 4,5)
    3. Clue cells (blue cells with dark blue spots)
    4. Positive whiff test with 10% KOH prep

II. Treatment

- Treated with antibiotics
    1. Metronidazole or clindamycin are the most commonly used ones.

1.4 – Treponema Pallidum

- Spirochete
- Screened for with RPR and VDRL
    1. RPR (rapid plasma regain): test of choice
    2. VDRL (venereal disease research laboratory): preferred when assessing CSF fluid for neurological involvement. Less used since you may have false positives in situations such as pregnancy, viral infections, rheumatic fever, and lupus.
    3. These tests detect anti-cardiolipin antibodies.
- Diagnosis confirmed with FTA-ABS and TPPA.
    1. FTA-ABS (fluorescent treponemal antibody absorption)
    2. TPPA (treponema pallidum particle agglutination)
    3. These tests detect antibodies to treponemal antigens.
    4. Results will be positive 2-3 weeks after infection and will remain positive even after treatment.
- Diagnosis can also be confirmed with direct tests such as dark field microscopy. A sample is taken from affected areas (thus can only be used in 1^{ary} and 2^{ndary}).
    1. PCR can also be used.

I. Presentation – Syphilis

- Primary
    1. Chancres: painless genital ulcers. There is no pain due to the necrosis also damages the nerve endings.
    2. Appears roughly 3 weeks after contact, heals in 3-6 weeks.
- Secondary
    1. Diffuse rash involving the palms and soles.
    2. Condyloma lata: painless lesion on genitals. May look like a wart with a lot of small, plateau-shaped bumps.
    3. Takes weeks – months to appear.
- Tertiary
    1. Gummas: soft growths with a firm center of necrosis,. These can grow anywhere, including the skin, bones, and internal organs.
    2. Obliterative endarteritis: damage of vaso vasorum → weakening of aorta → thoracic (ascending) aortic aneurysm.
    3. Arygle Robertson pupil (aka prostitute's pupil): Pupils can accommodate to distance but not to light.
    4. Tabes dorsalis: Neurosyphilis can cause slow degeneration of nerve roots, specifically the dorsal columns. Symptoms vary but can include severe pain, altered sensation, weakness, and loss of coordination and reflexes.
    5. Takes years to appear, can show up after a long latent period.
- Congenital
    1. Sabes shins: tibias bend forward.
    2. Saddle nose: short nose with an indented bridge.
    3. Mulberry molars: molars with enamel outgrowth.
    4. Hutchinson teeth: incisors with notches.
    5. Interstitial keratitis: inflammation of the cornea
    6. Deafness due to CN VIII damage.
    7. Symptoms generally appear within the first weeks/months of life, but can even take up to 5 years.

RECALL

Anatomy: vaso vasorum
These are the small blood vessels that supply the larger blood vessels.

Summary of clinical picture of syphilis

	Primary	Secondary	Tertiary	Congenital
Timing	- Appears 3 weeks after contact - Heals in 3-6 weeks	- Takes weeks – months to appear	- Takes years to appear - Can show up after a long latent people	- Generally appears within the 1st few weeks-months of life. - May take up to 5 years to appear
Symptoms	- Chancres	- Rash including palms and soles - Condyloma lata	- Gummas - Obliterative endarteritis - Argyl Robertson pupil - Tabes dorsalis	- Saber shins - Saddle nose - Mulberry molars - Hutchinson teeth - Interstitial keratitis - Deafness

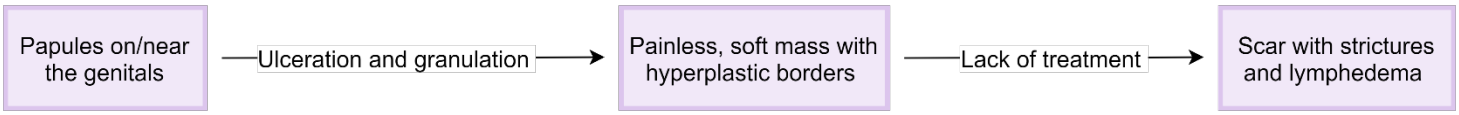
II. Treatment

- Penicillin is the 1st line of treatment.
    1. This is true even if the patient is allergic to penicillin! First you desensitize them, then you give them the penicillin for the syphilis.
- Prevent congenital disease by treating the mother during pregnancy, the earlier the better. The infection is transmitted through the placenta (not the birth canal) so early treatment is crucial.

1.5 – Klebsiella

- Gram negative bacillus
- Often associated with hospital-acquired pneumonia or UTIs but can also cause genital symptoms, referred to as granuloma inguinale.

I. Presentation



II. Treatment

- Can use 3rd generation cephalosporins, such as ceftriaxone or cefotaxime.
- Clindamycin or carbapenem can be used as well due to frequent drug resistance.

1.6 – Hemophilus Ducreyi

- Gram negative coccobacillus

I. Presentation

- Extremely painful genital ulcer, called chancroid.
    1. Mnemonic: it's so painful, you **do cry** (**du-creyi**).
- Painful inguinal lymphadenopathy
- Takes 4-10 days to appear
- May be asymptomatic, more likely in women.

II. Treatment

- Antibiotics, use ONE of those below
    1. Macrolides (ex: azithromycin)
    2. 3rd generation cephalosporins (ex: ceftriaxone)

1.7 – Test Yourself

1) Which is false about Neisseria gonorrhea?

a) It can cause adhesions by the liver
b) Arthritis is most likely in the knee
c) It causes a thick, white discharge
d) Infection in men stops in the prostate
e) Its complications include increased risk of ectopic pregnancy and infertility.

2) Which is false about Chlamydia trachomatis?

a) When diagnosed, you should also treat for Neisseria and vice-versa
b) It can cause Reiter syndrome
c) Arthritis is most likely in the sacroiliac joint
d) Types D-K are most associated with a thin, watery discharge
e) It never affects areas outside of the genitals

3) Which of these is NOT one of the Ansel criteria?

a) Response to metronidazole
b) Increased vaginal pH
c) Thin, grayish white discharge
d) Clue cells
e) Positive whiff test on 10% KOH prep

4) Match the symptom to the type of syphilis

a) Painless genital ulcer	b) Gummas	
c) Ascending aortic aneurysm	d) Saber shins	i) primary
e) Condyloma lata	f) Chancre	ii) secondary
g) Saddle nose	h) Mulberry molars	iii) tertiary
i) Hutchinson teeth	j) Argyle Robertson pupil	iv) congenital
k) Interstitial keratitis	l) Damage of vaso vasorum	
m) Rash affecting hands and feet	n) Tabes dorsalis	
o) Deafness		

5) Which statement is false?

a) A chancre is a painless genital ulcer
b) A chancroid is a painful genital ulcer
c) Klebsiella can cause genital papules
d) Hemophilus ducreyi causes chancroids
e) None of the above are false

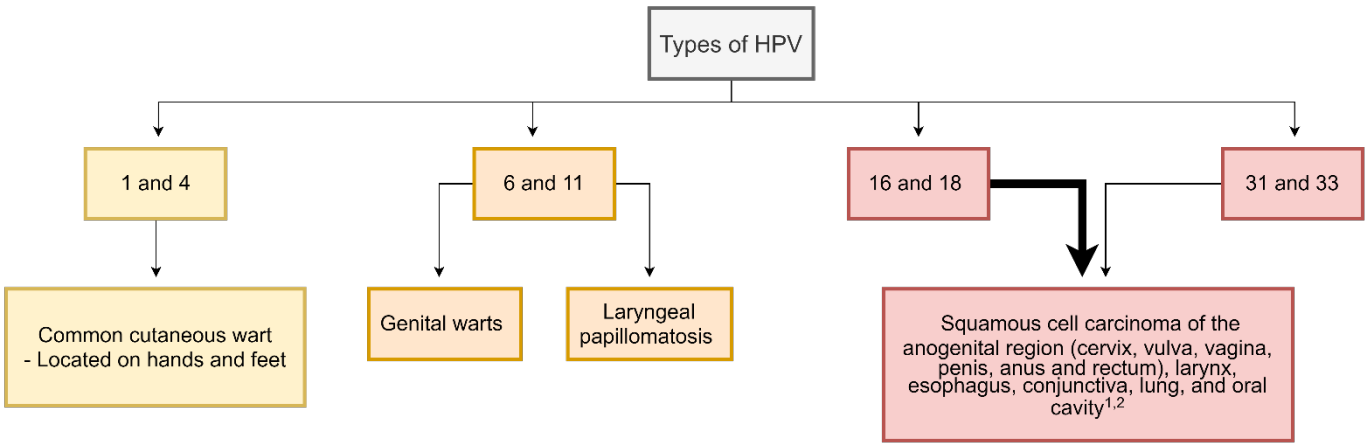
Section 2 – Viruses

2.1 – Human Papillomavirus (HPV)
2.2 – Herpes Simplex Virus (HSV)
2.3 – Test yourself

2.1 – Human Papilloma Virus (HPV)

- Double-stranded DNA virus
- Most common STD
- Can cause cancer by inhibiting stop signals in the cell cycle.

I. Presentation



[1] Types 16 and 18 are more strongly associated with cancer than types 31 and 33.
[2] Post-coital bleeding is a red flag for cancer.

II. Treatment

- Prevent with vaccination!
    1. Used to be given only to girls. In most countries it is now recommended to give it to boys as well due to the wide variety of associated carcinomas.
    2. Gardasil vaccine protects against the 4 most commonly carcinogenic subtypes (16, 18, 31, and 33)
- No treatment for virus itself

2.2 – Herpes Simplex Virus (HSV)

- Double-stranded, linear DNA virus
- Remains dormant in nerve root ganglia, which is why it is not entirely curable and can reappear.
    1. HSV 1 is dormant in the trigeminal ganglia.
    2. HSV 2 is dormant in the sacral ganglia.

I. Presentation

- In certain cases, either type of HSV can cause either presentation. The distinction below is based on the most common presentations and associations.
- HSV 1
    1. According to textbooks, it primarily affects the oral cavity and surrounding areas (particularly the lips). However, in reality it can also affect the anogenital region.
    2. Classically presents with cold sores on/near the lips, called herpes labialis.
    3. Can appear as herpetic whitlow on the fingers, common in dentists.
    4. Can cause keratoconjunctivitis by the eyes.
    5. Can cause temporal lobe encephalitis. The infection causes hemorrhage and necrosis in the inferior and median temporal lobes which may present with headache, fever, strange behavior, personality changes, olfactory hallucinations, and seizures.
    6. 1-2 weeks after infection, erythema multiforme lesions can appear on the hands and feet and advance proximally.

CLINICAL CORRELATION

Erythema multiforme
- Looks like a target.
- Classically associated with borreliosis.

- HSV 2
    1. According to textbooks, it primarily affects the anogenital region. However, in reality it can also affect the oral cavity and surrounding areas.
    2. Classically presents with painful inguinal lymphadenopathy and painful lesions appearing as clusters of vesicles with a red base.
    3. Can cause meningitis.
    4. Associated with neonatal herpes, which presents with various CNS pathologies. The child can get this while in its mothers uterus, thus making it a TORCH infection.

CLINICAL CORRELATION

TORCH infections
- These are infections which can be transmitted to the fetus during pregnancy.
- **T**oxoplasmosis
- **O**thers (syphilis, varicella, listeriosis, parvovirus B19)
- **R**ubella
- **C**MV
- **H**SV (also **H**BV and **H**IV)

II. Treatment

- The infection itself if not curable, thus symptoms can continually reoccur.
- Prevent breakouts with acyclovir and valacyclovir.

2.3 – Test Yourself

1) Match the presentation to the most common types of HPV associated with it

a) cutaneous wart
b) squamous cell carcinoma
c) genital wart
d) anogenital squamous cell carcinoma
e) laryngeal papillomatosis
f) condyloma acuminata
g) prostate cancer
h) cervical cancer
i) anal cancer

i) 1, 4
ii) 6, 11
iii) 16, 18
iv) 31, 33

2) Which is false?

a) HPV vaccine is given only to girls
b) Gardasil vaccine protects against subtypes 16, 18, 31, and 33
c) HPV can cause cancer in the oral cavity
d) Bleeding after sex is a red flag for cancer
e) AIDS increase the risk of developing cancer from HPV

3) Which is false?

a) HPV stands for human papilloma virus
b) HSV stands for herpes simplex virus
c) Both HPV and HSV can be eradicated completely from the host
d) HSV is one of the TORCH infections
e) HPV and HSV are DNA viruses

4) Which is false about HSV?

a) HSV 1 remains dormant in trigeminal ganglia
b) Can cause erythema multiforme
c) Symptoms of temporal lobe encephalitis include olfactory hallucinations and personality changes
d) HSV 2 remains dormant in the sacral ganglia
e) All lesions caused by HSV are completely painless


studyaid